REMARKS

In the Office Action dated June 9, 2005, claims 1-67 were examined with the result that all claims were rejected. The Examiner made the rejection final. In response, Applicant has filed a Request for Continuing Examination (RCE) and the following comments. In view of these comments, reconsideration of this application is requested.

In the Office Action, claims 1-67 were rejected under the Doctrine of Obviousness Type Double Patenting, as well as under 35 USC §102(e) and 35 USC §103(a) as being unpatentable in view of DeLuca et al U.S. 5,843,928. It is believed that all three of these rejections can be grouped together as Applicant believes the bases for patentability has a common theme which will overcome each of these three rejections.

The present invention is directed toward the use of 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 (referred to as 2MD) in a method for prophylaxis of a disease characterized by a need to increase bone strength. In order to demonstrate that 2MD improves the strength of bone whereas other vitamin D compounds do not, the inventors carried out some experiments which are reported at Tables 1 and 2 on pages 17 and 18 of the application as originally filed. It will be seen from the data that 2MD is unique in improving fracture strength, and 2MD shows results that are significantly better than the OVX control. In contrast, calcitriol (1α,25-dihydroxyvitamin D_3) showed no significant improvement in fracture strength of femur or vertebra. Applicant therefore believes that the 2MD compound is unexpectedly effective in increasing the strength of a bone, particularly when it is clear that other vitamin D compounds do not have this effect. The Examiner has admitted that the data in Tables 1 and 2 "clearly show that 2MD is effective in increasing bone mass and bone strength of normal female rats." Thus, Applicant believes the data reported in the specification supports the claimed invention.

The Examiner has noted, and Applicant agrees, that the basis of Applicant's arguments relies upon the difference between maintaining or increasing bone mass (the '928 patent) versus increasing the strength of a bone (the instant claims). As previously argued, increasing bone mass and/or the treatment of metabolic bone diseases is

significantly different from increasing the strength of a bone. Two bones having the same mass will not necessarily have the same strength due to the infrastructure of the bone itself. In other words, bone mass can be increased without necessarily increasing the strength of a bone due to the type of bone architecture being formed.

In support of Applicant's position, Applicant encloses a copy of an article by Riggs entitled "Causes of Age-Related bone Loss and Fractures" from a book entitled "Osteoporosis: Physiological Basis, Assessment, and Treatment," Elsevier Science Publishing Co., Inc. 1997, pages 7-16. In particular, Applicant refers the Examiner to pages 7 and 8 of this Riggs article. As discussed therein, there are three independent causes of bone fractures with the first being decreased bone density and the second being qualitative changes in bone structure. At the bottom of page 7, Riggs states:

> "Low bone density, therefore, is a necessary, but not a sufficient, cause of fracture, and the risk of fracture is a probabilistic function of a given level of bone density."

In other words, loss of bone mass by itself does not cause bone fractures, but is only indicative of the risk of a fracture given the amount of lost bone mass.

The second cause of bone fractures is changes in bone structure, and as can be seen on page 8 of the Riggs article, defects such as (1) accumulation of microfractures, (2) fatigue damage, (3) loss of trabecular connectivity, (4) failure to complete secondary mineralization, and (5) histologic osteomalacia are possible causes of changes in bone structure that impair bone strength. Thus, it is clear from the Riggs article that a bone with abnormal architecture is more likely to fracture than a bone with similar mass but intact or normal structure. Therefore, in order to increase bone strength, it is not only increasing bone mass which is important, but the type of bone formed that is also critical. Thus, increasing bone mass as stated in the '928 patent is not the same as increasing the strength of a bone as presently claimed.

Applicant has enclosed additional published articles with this response to further support its position that one can increase bone mass without increasing bone strength. For example:

(1) Sarkar et al, "Relationships Between Bone Mineral Density and Incident Vertebral Fracture Risk with Raloxifene Therapy," Journal of Bone and Mineral Research, Vol. 17, No. 1, 2002, pages 1-10. This article discusses the relationships between changes in bone mineral density (BMD) after raloxifene therapy, and the risk of vertebral fractures. Referring to the Abstract on page 1 of the article, it states:

> "Although low absolute values of bone mineral density (BMD) predict increased fracture risk in osteoporosis, it is not certain how well increases in BMD with antiresorptive therapy predict observed reductions in fracture risk."
>
> ***
>
> "The present data show that the measured BMD changes observed with raloxifene therapy are poor predictors of vertebral fracture risk reduction with raloxifene therapy."

In other words, increases in BMD do not necessary correlate to increased bone strength.

(2) Kleerekoper et al, "Evaluation and Treatment of Postmenopausal Osteoporosis," Chapter 49, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, Lippincott-Raven Publishers, Third Edition, 1996, pages 264-271. Referring to the last

paragraph of column 1 on page 269 of this article wherein a discussion of etidronate therapy is described, the author states:

> "Etindronate (Didronel®), the first bisphosphonate to become clinically available, has been used in several clinical trials to stabilize or increase bone mass and also to possibly reduce the vertebral fracture rate (14, 16-18). However, the effect on the vertebral fracture rate is still controversial and by no means well established."

In other words, although etidronate therapy increased bone mass, the data regarding improved bone strength was inconclusive.

Also referring to the last paragraph in column 2 on page 269 of the Kleerekoper et al article, sodium fluoride therapy is discussed. The author states:

> "Sodium fluoride is widely used as a therapy for post-menopausal osteoporosis. In doses of 50-75 mg/d, the increase in spinal bone mass achieved with sodium fluoride approximates 8% per year, twice that seen with either estrogen, calcitonin, or bisphosphonates. However, there is little evidence from properly conducted clinical trials that this increase in bone mass translates into a reduction in vertebral fractures."

Again, the author states that although sodium fluoride therapy increased bone mass, this increase in bone mass did not correlate to increased bone strength, i.e. a reduction in vertebral fractures.

(3) Riggs et al, "Bone Turnover Matters: The Raloxifene Treatment Paradox of Dramatic Decreases in Vertebral Fractures Without Commensurate Increases in Bone Density," Journal of Bone and Mineral Research, Vol. 17, No. 1, 2002, pages 11-13. Referring to the last sentence in the first full paragraph in column 1 on page 11 of this article, Riggs et al states:

> "These considerations have lead to the widespread belief that changes in BMD can serve as a surrogate for assessing treatment effects on fracture risk. Based mainly on the failure of large increases in BMD induced by sodium fluoride therapy to reduce fracture risk,[4] the U.S. Food and Drug Administration has not allowed surrogate markers for fractures such as BMD to be used as primary endpoints for assessing efficacy of anti-osteoporosis drugs. However, sodium fluoride therapy alters bone crystalline structure and reduces bone strength[5], so these results cannot be generalized to other treatments." (emphasis added)

Again, what Riggs et al is saying is that although sodium fluoride therapy increases bone mass, it also alters bone crystalline structure and therefore reduces bone strength. Thus, simply increasing bone mass does not necessarily increase bone strength.

(4) Meunier, "Evidence-Based Medicine and Osteoporosis: A Comparison of Fracture Risk Reduction Data from Osteoporosis Randomised Clinical Trials," IJCP, Vol. 53, No. 2, March 199. Referring

to the second column on page 126 under the heading "Fluoride," Meunier states:

> "In the discussion, Riggs et al noted that fluoride treatment increases cancellous bone mass but decreases cortical bone mass and increases skeletal fragility."

In other words, fluoride therapy increases bone mass, but also increases skeletal fragility.

In the Office Action, the Examiner points out that Applicant, in its specification, stated that a decrease in bone mass results in a consequent decrease in bone strength. The Examiner then states that although Applicant argues increasing bone mass is different from increasing bone strength, it appears that Applicant makes no difference between the two in its own specification. However, the Examiner will note that Applicant is referring to the loss of bone mass, not the increase of bone mass. In the published articles referred to above, all of the authors appear to agree that decreasing bone mass will result in decreased bone strength, and thus an increase in bone fragility. The opposite, is not true as noted above. Thus, Applicant's remarks regarding decreased bone mass are consistent with what is accepted in the art, and Applicant's argument regarding increased bone mass is also consistent with what is accepted in the art, as discussed above.

In the Office Action, the Examiner also rejects the claims under 35 USC §112, first paragraph as being non-enabled. At the bottom of page 2 and the top of page 3 of the Office Action, the Examiner states that although the data clearly show that 2MD is effective in increasing bone mass and bone strength of normal female rats, and thus enabling for rats, the claims are too broad and not enabling for all of the different species claimed, e.g. astronauts, athletes, pigs, hens, and fowl.

In response, however, it has long been recognized that a rat model is indicative of what might happen in humans, and has long been established as an acceptable model for correlating biological data to humans. Thus, data in rats has been for many years correlated to humans, and Applicant believes the rat data evidencing increasing bone strength in rats correlates to increasing bone strength in not only human beings, e.g. an astronaut or an athlete, but also in animals such as pigs and fowl. The particular species claimed are those for which increased bone strength would be advantageous. Clearly, an astronaut or an athlete would benefit from increased bone strength, and these persons are obviously also human beings. If the Examiner desires, Applicant can cite numerous published articles supporting its position that a rat model correlates to humans. The fact that rat models correlate to human models has long been accepted by those skilled in the art.

Finally, the Examiner indicated that there is no support for the prevention/prophylaxis of the diseases claimed. However, Applicant disagrees. The data in Figures 11, 12a, 12b, 13a and 13b clearly show that 2MD is effective in increasing bone mass of normal female rats. This is discussed in the specification at pages 20 and 21. In addition, the Examiner admitted in the Office Action that the data show increased bone strength. Thus, Applicant believes the data support use of 2MD for the prophylaxis or prevention of diseases characterized by a need to increase the strength of a bone.

The data clearly show that animals with normal bone mass were given 2MD and these animals had not only increased bone mass, but also increased bone strength. The animals did not have a metabolic bone disease, but instead were normal, healthy animals. Thus, the data clearly show that 2MD is effective in increasing bone mass and bone strength of normal female rats. This is the conclusion discussed on pages 20 and 21 of the application. Given that the animals had normal bone mass, and were not diseased, Applicant believes the data demonstrate that 2MD could be used as a prophylaxis or preventative measure against bone fractures. Thus, Applicant believes the Examiner should withdraw the §112, first paragraph rejection.

Finally, referring once again to the Riggs published article entitled "Causes of Age-Related Bone Loss and Fractures," Applicant notes that in the "Summary and Conclusions" section on page 14 of that article, Riggs states as follows:

> "...Because osteoporosis is more difficult to treat than to prevent, it will be important in the future to define these causal processes better and to intervene to correct them before fractures due to osteoporosis develop."

Thus, those skilled in the art clearly recognize that there is a difference between prevention and treatment. As a result, it is not obvious to one skilled in the art that a therapy which treats a disease will also prevent the disease.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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JOURNAL OF BONE AND MINERAL RESEARCH
Volume 17, Number 1, 2002

Relationships Between Bone Mineral Density and Incident Vertebral Fracture Risk with Raloxifene Therapy*

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ABSTRACT

Although low absolute values of bone mineral density (BMD) predict increased fracture risk in osteoporosis, it is not certain how well increases in BMD with antiresorptive therapy predict observed reductions in fracture risk. This work examines the relationships between changes in BMD after 1 year or 3 years of raloxifene or placebo therapy and the risk for new vertebral fractures at 3 years. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, 7705 postmenopausal women with osteoporosis were randomized to placebo or raloxifene 60 mg/day or 120 mg/day. Relationships between baseline BMD and changes in BMD from baseline with the risk of new vertebral fractures were analyzed in this cohort using logistic regression models with the raloxifene doses pooled. As has been observed in other populations, women with the lowest baseline lumbar spine or femoral neck BMD in the MORE cohort had the greatest risk for vertebral fractures. Furthermore, for any percentage change, either increase or decrease in femoral neck or lumbar spine BMD at 1 year or 3 years, raloxifene-treated patients had a statistically significantly lower vertebral fracture risk compared with placebo-treated patients. The decrease in fracture risk with raloxifene was similar across the range of percentage change in femoral neck BMD observed at 3 years; patients receiving raloxifene had a 36% lower risk of vertebral fracture compared with those receiving placebo. At any percentage change in femoral neck and lumbar spine BMD observed at 1 year, raloxifene treatment decreased the risks of new vertebral fractures at 3 years by 38% and 41%, respectively. The logistic regression model showed that the percentage changes in BMD with raloxifene treatment accounted for 4% of the observed vertebral fracture risk reduction, and the other 96% of the risk reduction remains unexplained. The present data show that the measured BMD changes observed with raloxifene therapy are poor predictors of vertebral fracture risk reduction with raloxifene therapy. (J Bone Miner Res 2002;17:1–10)

Key words: **bone mineral density, vertebral fracture, raloxifene**

INTRODUCTION

The World Health Organization's (WHO) definition of osteoporosis is based on the relationship between low bone mineral density (BMD) and "consequent increase in bone fragility and susceptibility to fracture."[1] An increased risk of a new vertebral fracture in postmenopausal women is predicted by a low lumbar spine BMD,[2] an increase in age,[3] and the existence of prevalent vertebral fractures.[4,5] Even after adjustment for age, both low baseline BMD and prevalent vertebral fractures are predictive of an increased risk of subsequent vertebral fractures.[3,6] Baseline BMD is useful for determining if patients are candidates for therapeutic intervention[1] because it predicts the future risk of an osteoporotic fracture, the ultimate clinical outcome.

As the number of therapeutic choices available for prevention and treatment of osteoporosis has increased, there is a growing need to understand the relationship between treatment-induced changes in BMD and fracture risk reduc-

*Portions of this work were presented in part at the meeting of the 1999 American Society for Bone and Mineral Research, 1999; the meeting of the World Congress of Osteoporosis, 2000; and the meeting of the American College of Rheumatology, 2000.

Dr. Somnath Sarkar, Dr. Bruce H. Mitlak, Dr. Mayme Wong, Dr. John L. Stock, and Dr. Kristine D. Harper have financial interests in the forms of corporate appointments and stock ownership in Eli Lilly and Company. Dr. Dennis M. Black does consultant work for Eli Lilly and Company.

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tion. However, it is not known how well treatment-induced changes in BMD are correlated with or are predictive of the reductions in fracture risk observed with therapy. Although increases in BMD resulting from antiresorptive therapies differ greatly in magnitude, reductions in vertebral fracture risk are quite similar. For example, in postmenopausal women without prevalent vertebral fractures, raloxifene, 60 mg/day for 3 years,[7] and alendronate, given for an average of 4.2 years,[8] increased lumbar spine BMD by 2.8% and 6.8%, respectively, compared with placebo. In these same studies, raloxifene, 60 mg/day, decreased the absolute risk of new vertebral fractures by 2.4%, and the relative risk by 55% (95% CI, 29% and 71%),[9] and alendronate decreased the absolute risk of new vertebral fractures by 1.7% and the relative risk by 44% (95% CI, 20% and 61%).[8] The relationship between changes in BMD and fracture risk may be quantitatively different for the various therapeutic agents evaluated, because these agents act to inhibit bone resorption through different mechanisms.[10]

For assessing the effects of a therapeutic intervention in patient management and to reduce the cost and length of clinical trials, biological markers often are used as surrogates for those actual clinical outcomes that are observed in long trials with a large number of subjects. The effect of a therapeutic intervention on a surrogate endpoint must reliably predict the effect on the actual clinical outcome in order for the surrogate to be considered an acceptable substitute.[11] It is uncertain whether monitoring the changes in BMD observed with antiresorptive therapy can be used as reliable surrogates for predicting fracture efficacy.[12–14] However, several reports suggest that the increases in BMD during antiresorptive therapy may be poor estimates of the resultant fracture risk reduction observed with bisphosphonates, estrogen, and raloxifene.[12–16]

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial evaluated the effects of raloxifene, a selective estrogen receptor modulator, on the risk of new vertebral fractures and changes in BMD in 7705 postmenopausal women with osteoporosis.[7] Because of the large size of the MORE study cohort, it is possible to analyze the relationships between BMD and vertebral fracture risk. These analyses will determine if the relationships between baseline BMD and vertebral fracture risk in the MORE cohort are similar to those reported in other study populations. Other analyses will examine whether increases in BMD with raloxifene can predict vertebral fracture risk reduction and if vertebral fracture risk reduction observed with raloxifene can be attributed to changes in BMD. The primary overall objective was to determine whether changes in BMD could be used as possible surrogate endpoints to monitor clinical response to raloxifene therapy.

MATERIALS AND METHODS

The design of the 3-year MORE trial was described previously.[7] A total of 7705 women with osteoporosis, who were at least 2 years postmenopausal, were randomized to either placebo or raloxifene, 60 mg/day or 120 mg/day. All women received daily calcium (500 mg) and vitamin D (400–600 IU) supplements. Women were excluded if they had bone disease other than osteoporosis, substantial postmenopausal symptoms, abnormal uterine bleeding, or endometrial carcinoma. Additionally, women who had pathological fractures, women for whom satisfactory thoracic and lumbar spine radiographs could not be obtained, and women with fewer than two lumbar vertebrae that were evaluable were excluded. Complete inclusion and exclusion criteria and procedures for subject recruitment and follow-up were described previously.[7]

BMD was assessed in the femoral neck and lumbar spine at baseline and at yearly intervals using dual-energy X-ray absorptiometry (DXA). A central reading facility (Osteoporosis and Arthritis Research Group [OARG], University of California, San Francisco, CA, USA) performed quality assurance of the longitudinal and cross-calibration adjustments to the DXA machines and patients' BMD measurement data and provided correction factors to adjust for differences between sites and performance of densitometers over time. To assess vertebral fractures, spinal radiographs obtained at baseline, 2 years and 3 years, were analyzed using a combination of semiquantitative (SQ) readings and quantitative morphometric (QM) analysis. A fracture identified by SQ assessment was followed with another independent binary SQ assessment and a QM measurement. An adjudicated fracture was reported if it was confirmed by at least two of the three determinations. The criterion for diagnosis of a new vertebral fracture was based on a reduction in the anterior, middle, and/or posterior vertebral height of >20% and at least 4 mm, compared with the baseline radiograph. All vertebral radiographs were assessed at a central quality assurance center (OARG) by radiologists blinded to treatment group assignment but not to the temporal sequence of the radiographs. Because the BMD values obtained from fractured vertebrae would be artificially high, all previous BMD values from vertebrae with visually observable fractures on the DXA screen were excluded from the analyses.

Women were considered to have osteoporosis if they had a baseline femoral neck or lumbar spine BMD of >2.5 SD below the normal, peak bone mass of premenopausal women (T score < -2.5), or had at least one moderate or two mild prevalent vertebral fractures irrespective of baseline BMD. The results from both doses of raloxifene were pooled to increase the statistical power of the present analyses.

Baseline BMD and vertebral fracture risk

Using logistic regression analysis methods, we examined the relationship between baseline femoral neck and lumbar spine BMD and the risk of having at least one new vertebral fracture over 3 years. The presence of any incident vertebral fracture was considered a binomial (yes/no) response and baseline BMD was considered a continuous covariate. The model included treatment (pooled raloxifene and placebo), baseline BMD, and treatment effect-by-baseline BMD interaction as fixed effects. If the interaction term is significant, this indicates that the treatment effect (fracture risk) is dependent on the baseline BMD, whereas a nonsignificant interaction term indicates that the observed fracture risk is independent of baseline BMD. This model estimated the risk of a new vertebral fracture for each treatment group

(pooled raloxifene or placebo) over the broad range of baseline BMD values. The absolute risk of a new vertebral fracture for the raloxifene and placebo groups and the relative risk between groups, along with the 95% CIs, were calculated from this model.

Percentage change in BMD and vertebral fracture risk

The relationships between the percentage change in lumbar spine or femoral neck BMD from baseline to the 1-year or 3-year endpoint and the risk of having at least one new vertebral fracture at 3 years were tested by logistic regression analysis. The presence of any new vertebral fracture was considered a binomial (yes/no) response and changes in BMD were considered as continuous covariates. In these models, treatment (pooled raloxifene and placebo), percentage change in BMD, and the treatment effect-by-percentage change in BMD interaction were fixed effects. The models estimated the risk of a new vertebral fracture for each treatment group (pooled raloxifene or placebo) over the broad range of percentage changes in BMD. Additionally, the models estimated the contribution of a change in BMD to the reduced risk of incident vertebral fractures observed with raloxifene (treatment effect). The absolute risk of a new vertebral fracture for the raloxifene and placebo groups and the relative risk between groups, along with the 95% CI, were calculated from the fitted models.

These analysis models also were used to examine the relationships between the risk of having at least one new vertebral fracture at 3 years with the absolute endpoint BMD values and the absolute BMD changes in the lumbar spine and femoral neck at 3 years.

Statistical analyses

A generalized linear modeling technique was used to relate the risk (binomial regression with logit link) of a new vertebral fracture with either baseline BMD or percentage change in BMD for each patient.[17] These logistic regression models included a treatment dummy variable (pooled raloxifene groups and placebo), with baseline BMD (or percentage change in BMD), as continuous variables. Changes in BMD from baseline to 3 years or from baseline to 1 year were calculated after imputing missing values by the last observation carried forward (LOCF) method. Although logistic regression models are used commonly to estimate odds ratios (ORs), this method can be used to calculate absolute and relative risks for vertebral fractures. The 95% CI for absolute and relative risks for vertebral fractures were calculated using the Mantel Haenszel large sample method. To quantify the amount of fracture risk reduction attributed to raloxifene that is explained by a change in BMD, the relative risk reduction adjusted for the change in BMD was compared with the actual observed relative risk reduction, that is, before adjustment for change in BMD. This method, similar to that of Freedman,[18] cannot be used effectively if there is a significant interaction between the percentage change in BMD and treatment. According to the study protocol, the interaction was tested at the 10% significance level in this model. A nonsignificant interaction term indicates that the effects of treatment and percentage change in BMD on the observed fracture risk are independent, whereas a significant interaction term indicates that the treatment effect (fracture risk) is dependent on the percentage change in BMD. In cases in which the interaction term was significant, the treatment effect (fracture risk) cannot be quantified as a single value.

In a graphical presentation of the relationship, the continuous values of fracture risks observed at the continuous percentage changes in BMD were plotted as separate curves with 95% CI for each treatment group. If the placebo and raloxifene curves with their respective 95% CI bands were superimposed on each other, it was inferred that the percentage change in BMD explained the observed reduction in fracture risk. On the other hand, if the placebo and raloxifene curves with their respective 95% CI bands did not overlap in the graph, it was inferred that the percentage change in BMD did not explain the decrease in fracture risk observed with raloxifene therapy. From these graphs, the percentage of fracture risk reduction between the raloxifene and placebo groups was estimated at the lower 25th and median 50th percentiles and the upper 75th percentile of changes in BMD and these discrete data were shown separately in tables.

RESULTS

The baseline characteristics of the women in the MORE trial were previously reported in detail[7] and summarized briefly in Table 1. The women in the study population had a mean age of 66.5 years, a mean body mass index (BMI) of 25.2 kg/m^2, and were a mean of 18.7 years postmenopausal. Prevalent vertebral fractures were present in 37.3% of the total study population. At randomization, the lumbar spine and femoral neck BMD were 0.82 ± 0.13 g/cm^2 and 0.62 ± 0.08 g/cm^2 (mean ± SD), respectively. There were no statistically significant differences in the baseline characteristics between the placebo and the raloxifene groups.

Percentage changes in BMD at the lumbar spine or femoral neck compared with placebo were not significantly different between the two doses of raloxifene at any time point in the MORE study. The incidence of new vertebral fractures and the relative risk of a new vertebral fracture compared with placebo were not significantly different between the raloxifene groups at 3 years.

Baseline BMD

Women in the MORE cohort with the lowest baseline femoral neck or lumbar spine BMD had the greatest risk of a new vertebral fracture (Fig. 1). Baseline BMD measurements at both the femoral neck and the lumbar spine were significantly ($p < 0.001$) related to the risk of a new vertebral fracture at 3 years, as determined by logistic regression analysis (Fig. 1). Among women in the placebo group, a 1 SD decrease in baseline femoral neck BMD and in baseline lumbar spine BMD significantly increased the risk of a new vertebral fracture 1.5-fold and 2-fold, respectively, at 3 years.

The efficacy of raloxifene in decreasing fracture risk was similar across the broad range of baseline femoral neck BMD (interaction, $p = 0.76$; Fig. 1A). Raloxifene decreased

TABLE 1. BASELINE CHARACTERISTICS OF 6828 POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS IN THE MORE TRIAL[a]

Characteristics	Placebo (n = 2292)	Raloxifene, 60 mg/day (n = 2259)	Raloxifene, 120 mg/day (n = 2277)	Overall p value[b]
Age (year)	66.6 ± 7.0	66.4 ± 6.9	66.2 ± 7.1	0.168
Years since menopause	18.7 ± 8.3	18.6 ± 8.5	18.2 ± 8.2	0.129
BMI (kg/m²)	25.3 ± 4.0	25.3 ± 4.0	25.2 ± 4.0	0.994
Prevalent vertebral fracture	36.4%	37.9%	37.9%	0.477
Previous hysterectomy	22.1%	23.3%	21.6%	0.355
Previous estrogen use	28.5%	28.7%	28.3%	0.595
Femoral neck BMD[c] (g/cm²)	0.62 ± 0.08	0.62 ± 0.08	0.62 ± 0.08	0.264
NHANES T score	−2.74 ± 0.66	−2.72 ± 0.65	−2.75 ± 0.63	0.260
Lumbar spine BMD[c] (g/cm²)	0.81 ± 0.14	0.82 ± 0.13	0.81 ± 0.13	0.552
T score	−2.58 ± 1.14	−2.55 ± 1.09	−2.58 ± 1.10	0.546

NHANES, Third National Health and Nutrition Examination Survey.

[a] Of the 7705 women enrolled in the MORE trial, a total of 6828 women had at least 1 post-baseline BMD determination. Data are presented as mean ± SD unless otherwise indicated.

[b] p Value between all groups.

[c] BMD (adjusted values) measured at randomization.

the risk of incident vertebral fractures by approximately 41% compared with the placebo group at every baseline value of femoral neck BMD ranging from 0.50 to 0.75 g/cm², which represents the 5th-95th percentiles of the population. In contrast, the effect of raloxifene treatment on fracture risk reduction was different at each percentile of baseline lumbar spine BMD (interaction, $p = 0.08$; Fig. 1B). Women in the lower percentiles for baseline lumbar spine BMD had greater decreases in fracture risk with raloxifene treatment compared with women in the upper percentiles (Fig. 1B).

Percentage changes in BMD at 3 years

At 3 years, raloxifene increased femoral neck and lumbar spine BMD by 2.2% and 2.7%, respectively, compared with placebo. These increases in BMD were relatively modest in comparison with the robust 40% reduction in vertebral fracture risk at 3 years. To explain this disparity between the BMD increases and fracture risk reduction and to test the hypothesis that changes in BMD can predict fracture risk reduction, the relationships between percentage changes in femoral neck and lumbar spine BMD and the observed fracture risk reduction were assessed using logistic regression models.

The raloxifene group had a statistically significantly lower vertebral fracture risk compared with the placebo group at any percentage change in femoral neck BMD from −7.3 to 10.1%, which represents the 5th-95th percentiles of the population. This relationship is shown graphically in Fig. 2A, as the raloxifene curve is below the placebo curve at all values of femoral neck BMD. Because there was no statistically significant interaction between treatment and percentage change in femoral neck BMD, the interaction effect was dropped from the logistic regression model (interaction, $p = 0.81$).

The relative risk of vertebral fracture with raloxifene was decreased by approximately 36%, at the lower 25th and median 50th percentiles and the upper 75th percentile of the

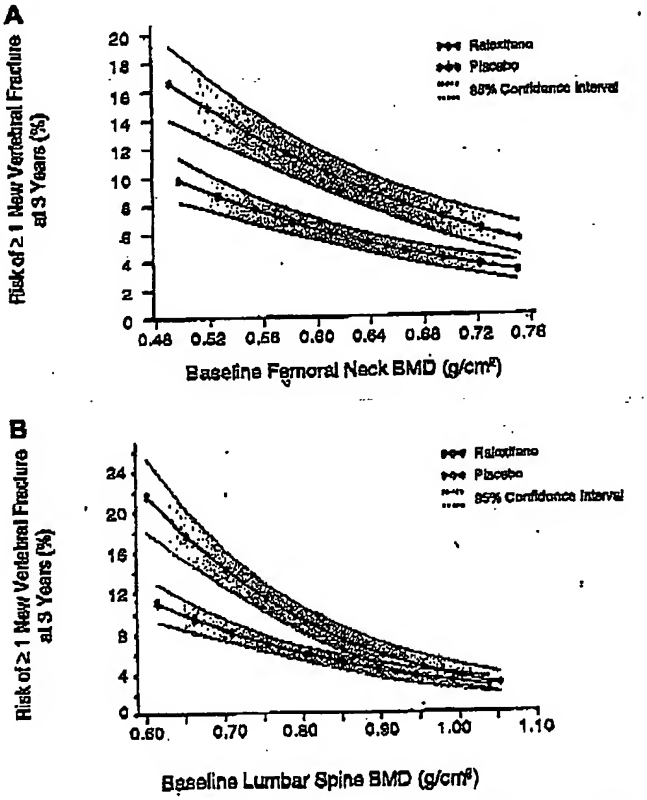

FIG. 1. (A) Logistic regression analysis curves of baseline femoral neck BMD and the risk of new vertebral fractures with 95% CIs for the pooled raloxifene (circles) and placebo (stars) groups. (B) Logistic regression analysis curves of baseline lumbar spine BMD and the risk of new vertebral fractures with 95% CIs for the pooled raloxifene (circles) and placebo (stars) groups.

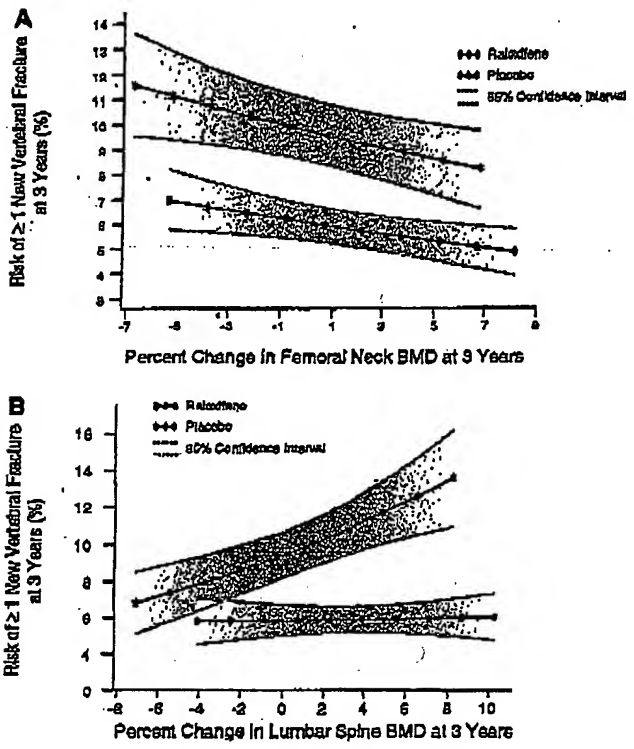

FIG. 2. (A) Logistic regression analysis curves of the percentage change in femoral neck BMD at 3 years and the risk of new vertebral fractures with 95% CIs for the pooled raloxifene (circles) and placebo (stars) groups. (B) Logistic regression analysis curves of the percentage change in lumbar spine BMD at 3 years and the risk of new vertebral fractures with 95% CIs for the pooled raloxifene (circles) and placebo (stars) groups.

percentage change in femoral neck BMD (Table 2). For example, in the 75th percentile of the population, which corresponds to a 4.2% increase in femoral neck BMD from baseline, the relative risk of a new vertebral fracture was 0.64. This same 36% reduction in vertebral fracture risk also was observed in the 25th percentile of the population, which corresponds to a 1.9% decrease in femoral neck BMD (Table 2). The percentage of increase in femoral neck BMD at 3 years accounted for 4% of the total vertebral fracture risk reduction observed with raloxifene. This value was calculated by subtracting the relative risk reduction for vertebral fractures with raloxifene treatment before and after adjustment for the percentage change in femoral neck BMD.

The raloxifene group consistently had a lower fracture risk compared with the placebo group at any percentage change in lumbar spine BMD from −4.1% to 10.8%, which represents the 5th-95th percentiles of the population (Fig. 2B). However, the curves for the placebo and raloxifene groups have markedly different slopes, suggesting varying degrees of fracture risk reduction with different percentage changes in lumbar spine BMD. Indeed, the interaction effect between treatment and percentage change in lumbar spine BMD was statistically significant ($p = 0.01$). In the placebo group, the fracture risk increased as the lumbar spine BMD increased, and in the raloxifene group, the fracture risk changed very little over a wide range of percentage changes in lumbar spine BMD, resulting in a curve with a slope close to zero (0.0052).

At the 75th percentile of the population, which corresponds to a 6.1% increase in lumbar spine BMD, the risk of an incident vertebral fracture was decreased by 52% with raloxifene therapy (Table 2). In contrast, raloxifene decreased the risks of incident vertebral fractures by 39% and 46% at the 0.3% and 3.1% increases in lumbar spine BMD, which correspond to the 25th and 50th percentiles of the population, respectively. This logistic regression analysis showed that the percentage change in lumbar spine BMD accounts for a fraction of the total reduction in the relative risk of new vertebral fractures. However, this fraction cannot be quantified accurately because of the significant interaction effect.

The upward sloping curve for the placebo group (Fig. 2B) suggested that increased lumbar spine BMD was associated with an increased vertebral fracture risk. In the placebo group, women who had an increased number of new vertebral fractures also had a significant percentage increase in lumbar spine BMD (overall, $p = 0.0001$). The mean change in lumbar spine BMD was found to be significantly different between women with no new fractures (Fig. 3) compared with women who had one, two, or three or more new fractures ($p < 0.05$, all between-group comparisons). The relationship between the percentage change in femoral neck BMD and the number of new vertebral fractures was not statistically significant.

Percentage changes in BMD at 1 year

Because the increasing number of new vertebral fractures in the placebo group (Fig. 3) may have obscured the relationship between 3-year changes in lumbar spine BMD and relative risk of fracture (Fig. 2B), similar logistic regression analyses were performed using a 1-year change in lumbar spine BMD. At 1 year, raloxifene treatment increased femoral neck and lumbar spine BMD by 1.3% and 2.1%, respectively, compared with placebo. The interaction effect between treatment and 1-year percentage change in lumbar spine BMD was not statistically significant ($p = 0.23$) and thus was dropped from the logistic regression model.

The raloxifene group consistently had a lower fracture risk compared with the placebo group at any 1-year percentage change in femoral neck or lumbar spine BMD from the 5th-95th percentile (Fig. 4). The regression analysis curve for the relative risk of fracture with a 1-year percentage change in femoral neck BMD (Fig. 4A) was similar to that observed with a 3-year percentage change in femoral neck BMD (Fig. 2A). The relative risk of incident vertebral fractures was decreased by 38% at the 25th and 50th percentiles and the 75th percentile of a 1-year change in femoral neck BMD (Table 3). Thus, women at the 25th percentile, who had a 1.2% decrease in femoral neck BMD, had similar reduction in vertebral fracture risk as women at the 75th percentile, who had a 4.0% increase in femoral neck BMD. Lumbar spine BMD at 1 year was increased by 0.4% at the 25th percentile of the population and by 4.7% at the

TABLE 2. RELATIONSHIP BETWEEN PERCENTAGE CHANGE IN FEMORAL NECK AND LUMBAR SPINE BMD AT 3 YEARS AND RISKS OF NEW VERTEBRAL FRACTURES

	BMD		New vertebral fractures		
			Absolute risk (95% CI)		Relative risk (95% CI)
	Percentile	% Change	Placebo	Raloxifene	
Femoral Neck[a]	25th	−1.86	0.10 (0.09,0.11)	0.06 (0.06,0.07)	0.64 (0.52,0.76)
	50th	1.08	0.09 (0.08,0.10)	0.06 (0.05,0.07)	0.64 (0.52,0.76)
	75th	4.21	0.08 (0.07,0.10)	0.05 (0.05,0.06)	0.64 (0.51,0.76)
Lumbar Spine[b]	25th	0.30	0.10 (0.08,0.11)	0.06 (0.05,0.07)	0.61 (0.49,0.74)
	50th	3.13	0.11 (0.09,0.12)	0.06 (0.05,0.07)	0.54 (0.44,0.65)
	75th	6.06	0.12 (0.10,0.14)	0.06 (0.05,0.07)	0.48 (0.36,0.59)

[a] The interaction effect between treatment group and percentage change in femoral neck BMD at 3 years was not statistically significant ($p = 0.81$) and was dropped from the logistic regression model.
[b] The interaction effect between treatment group and percentage change in lumbar spine BMD at 3 years was statistically significant ($p = 0.01$).

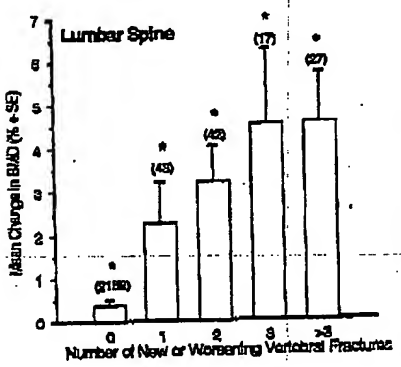

FIG. 3. Women in the placebo group who had an increasing number of new or worsening vertebral fractures also had an apparent increase in lumbar spine BMD at 3 years (overall, $p = 0.001$). This overall significance was not found for the percentage change in femoral neck BMD. The mean difference in lumbar spine BMD for women with no fractures also was significantly different from women with one, two, or three or more fractures (all comparisons between groups, $p < 0.05$). Numbers above the bars (n) indicate the number of women in that category. *Statistically significant change in BMD from baseline to 3 years.

75th percentile; yet, the risk of incident vertebral fractures was decreased by 41% with raloxifene treatment, irrespective of the percentage of increase in BMD (Table 3).

All of these logistic regression analyses were performed with the baseline or percentage change in femoral neck and lumbar spine BMD with raloxifene, 60 mg/day, the currently marketed dose, and the statistical inferences were identical (data not shown). Logistic regression models were used to analyze the relationships between the observed reduction in fracture risk with raloxifene, with the absolute endpoint BMD values and the absolute changes in BMD at the lumbar spine and femoral neck after 3 years. The results on vertebral fracture risk reduction with absolute endpoint BMD values and absolute change in BMD (data not shown) were similar to that observed with percentage change in BMD.

DISCUSSION

The relationships between baseline BMD and vertebral fracture risk in placebo-treated women in the MORE cohort were consistent with the relationships observed in untreated women in prospective, observational studies.[19] For example, with a 1 SD decrease in femoral neck BMD, the relative risk of vertebral fracture was increased 1.5-fold in the MORE cohort and 1.8-fold in other studies.[2,20] Logistic regression analysis confirmed that baseline femoral neck or lumbar spine BMD predicted vertebral fracture risk, and women with the lowest baseline BMD had the greatest fracture risk. In this study, raloxifene therapy consistently reduced vertebral fracture risk compared with placebo, irrespective of the baseline BMD value at the femoral neck or lumbar spine, as the regression curves for the raloxifene group were consistently below the curves for the placebo group.

Although baseline BMD values were predictive of subsequent fracture risk in this study, the percentage changes in BMD after raloxifene therapy were found to be poorly predictive of the fracture risk reduction observed with raloxifene therapy, contrary to our hypothesis. Raloxifene-treated patients consistently showed lower fracture risk than placebo, irrespective of the percentage changes in femoral neck BMD observed at 1 or 3 years, as the raloxifene curves were consistently below the placebo curves, and the curves were not superimposed. However, the changes in femoral neck BMD at 1 year or 3 years did not predict the fracture benefit with raloxifene, because the observed fracture risk reduction was very similar over the range of BMD changes. In fact,

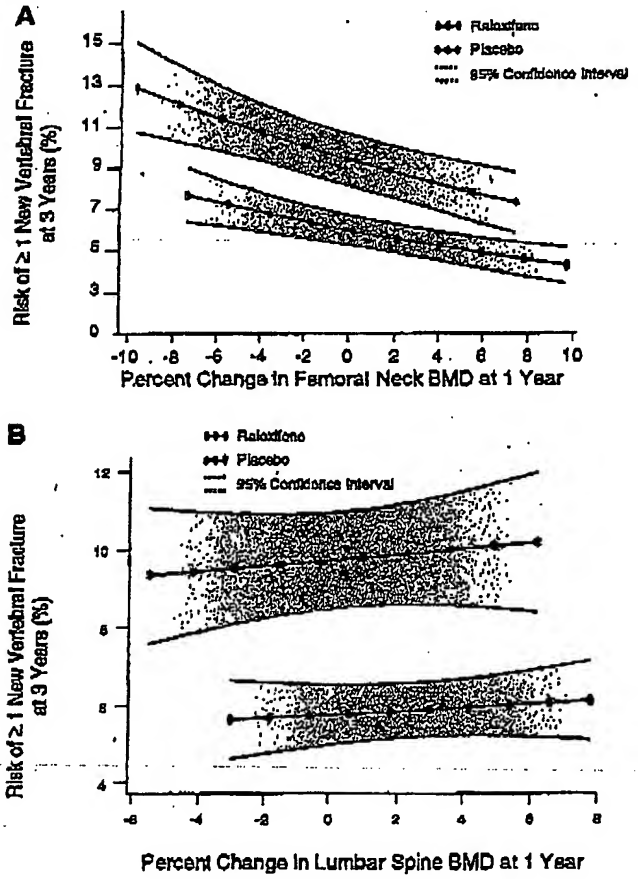

FIG. 4. (A) Logistic regression analysis curves of the percentage change in femoral neck BMD at 1 year and the risk of new vertebral fractures with 95% CIs for the pooled raloxifene (circles) and placebo (stars) groups. (B) Logistic regression analysis curves of the percentage change in lumbar spine BMD at 1 year and the risk of new vertebral fractures with 95% CIs for the pooled raloxifene (circles) and placebo (stars) groups.

the 1-year and 3-year changes in femoral neck BMD accounted for about 4% of the fracture risk reduction with raloxifene therapy. Similar results were observed with changes in lumbar spine BMD at 1 year. The relationships between the vertebral fracture risk reduction with raloxifene at 3 years and the absolute endpoint BMD values or the absolute BMD changes at 3 years were similar to that observed with the 3-year percentage changes in lumbar spine and femoral neck BMD. However, counterintuitive changes were observed in the lumbar spine BMD at 3 years. In the raloxifene group, the fracture risk was similar at all percentage changes in lumbar spine BMD at 3 years, as depicted by the flat curve, whereas in the placebo group, the fracture risk increased with increasing BMD. Therefore, lumbar spine BMD at 3 years was poorly predictive of the vertebral fracture risk at 3 years. Also, the 3-year change in lumbar spine BMD only accounted for a fraction of the observed vertebral fracture risk reduction with raloxifene, but this risk reduction could not be reliably calculated, because of the aberrant changes in the placebo group. Nevertheless, given the markedly different slopes for the change in lumbar spine BMD between the raloxifene and placebo groups, raloxifene-treated patients with the greatest increases in lumbar spine BMD had the greatest reduction in fracture risk.

Accuracy and reproducibility errors in BMD measurements may have contributed to the relationships observed between BMD and vertebral fracture risk in these analyses. In this study, the accuracy and reproducibility of the BMD measurements were verified according to established protocols.[21,22] In cross-sectional studies of postmenopausal women of various age groups, the accuracy of lumbar spine BMD measurements decreases with increasing age because of spinal osteoarthritis in elderly populations.[23] The accuracy errors for posterior-anterior spine DXA can vary from 4% to 10%, and the accuracy error for proximal femur DXA measurements is estimated as 6%.[24] The short-term and long-term reproducibility errors are greater in the femoral neck than in the lumbar spine.[24,25] Errors may result from differences between DXA machines, longitudinal drifts within machines, and placement of the patient on the machine for measurements. Even after statistical adjustments for reproducibility errors, changes in femoral neck BMD accounted for <10% of the observed vertebral fracture risk reduction after 3 years in the MORE trial.[26]

In addition, the amount of fat to lean body mass surrounding the tissues could affect the tissue density gradient assessed by DXA and influence the accuracy and reproducibility of BMD measurements. Postmenopausal women with greater body weight and fat or lean body mass were found to have higher lumbar spine, hip, and femoral neck BMD.[27,28] In this study, the mean weight and mean BMI of women in the pooled raloxifene group were increased by 0.3 kg and 0.3 kg/m^2, respectively, compared with the placebo group at 3 years ($p < 0.001$ for both endpoints). It is not known if these slight increases in BMI and weight observed with raloxifene contribute to the imprecision of the BMD measurements or observed decrease in vertebral fracture risk.

Lumbar vertebrae with fractures that were visually observable on the DXA screen were excluded from the BMD analyses in the MORE trial because accurate BMD measurements could not be obtained. It is possible that microarchitectural deformities in the vertebrae, which were not visually evident, could accumulate over time and contribute to the apparent increase in the overall lumbar spine BMD measurements and ultimately accumulate to a fracture.[29–31] In addition, the presence of degenerative conditions of the spine such as osteophytosis and end plate sclerosis could contribute to the variation in lumbar spine BMD measurements[32] and hence the accuracy of fracture risk prediction. However, the variations in BMD measurements caused by degenerative changes in the vertebrae would be expected to affect both treatment groups equally.

The presence of fewer microarchitectural deformities or degenerative changes at 1 year compared with 3 years may contribute to greater accuracy in predicting fracture risk reduction, making the percentage change in lumbar spine BMD at 1 year a better predictor, although still poor, than the change at 3 years. The relationship between BMD and

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Received in original form February 26, 2001; in revised form July 27, 2001; accepted September 28, 2001.

Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism

Third Edition

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Lippincott - Raven
PUBLISHERS
Philadelphia • New York

Printed in the United States of America

9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data
Primer on the metabolic bone diseases and disorders of mineral metabolism / editor, Murray J. Favus : associate editors, Sylvia Christakos ... [et al.]. — 3rd ed/
p. cm.
"An official publication of the American Society for Bone and Mineral Research"—Cover.
Includes bibliographical references and index.
ISBN 0-397-51763-7
1. Bones—Metabolism—Disorders. 2. Mineral metabolism—Disorders. I. Favus, Murray J. II. Christakos, Sylvia. III. American Society for Bone and Mineral Research.
[DNLM: 1. Bone Diseases, Metabolic. 2. Bone and Bones—metabolism. 3. Minerals—metabolism. WE 250 P953 1996]
RC930.P75 1996
616.7'16—dc20
DNLM/DLC
for Library of Congress 96-16184

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49. Evaluation and Treatment of Postmenopausal Osteoporosis

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Osteoporosis is a disease characterized by low bone mass and the development of nontraumatic or atraumatic fractures as a direct result of the low bone mass. A nontraumatic fracture has been arbitrarily defined as one occurring from trauma equal to or less than that of a fall from a standing height. In the preclinical state, the disease is characterized simply by a low bone mass without fractures. This totally asymptomatic state is often termed osteopenia. Osteoporosis and osteopenia are the most common metabolic bone diseases in the developed countries of the world, whereas osteomalacia may be more prevalent in underdeveloped countries where nutrition is suboptimal. To be able to evaluate more fully the prevalence and incidence of osteoporosis worldwide, the World Health Organization (WHO) recently convened an expert panel to define osteoporosis on the basis of bone mass measurement (1). Table 1 provides the diagnostic categories for women that were established by that panel. Osteoporotic fractures may affect any part of the skeleton except the skull. Most commonly, fractures occur in the distal forearm (Colles' fracture), thoracic and lumbar vertebrae, and proximal femur (hip fracture).

The epidemiology of osteoporosis is detailed in Chapter 44 and is only briefly summarized here. The incidence of osteoporotic fractures increases with age, is higher in whites than in blacks, and is higher in women than in men. The female to male ratio is 1.5:1 for Colles' fractures, 7:1 for vertebral fractures, and 2:1 for hip fractures. Because most osteoporotic fractures do not require admission to the hospital, it is difficult to obtain precise figures on the true prevalence of this disease. Almost without exception, a hip fracture requires admission to a hospital, and current estimates indicate that there are 275,000 new osteoporotic hip fractures each year in the United States. It has been estimated that after menopause, a woman's lifetime risk of sustaining an osteoporotic fracture is one in three. Regrettably, despite improvements in surgical techniques and anesthesiology, most hip fractures require surgical intervention on a nonelective basis, and there is a 15% to 20% excess mortality after an osteoporotic hip fracture. Perhaps more important, after such fractures, less than one third of the patients are restored to their prefracture functional state within 12 months of the fracture. Most patients require some form of ambulatory support, and many require institutional care. Current estimates indicate that each new case of osteoporotic hip fracture costs $40,000, and the annual expenditure for short-term care after an osteoporotic hip fracture already exceeds $8 billion. Chapter 50 provides more details on the special problems posed by osteoporotic fractures of the hip.

PATHOGENESIS

Once peak adult bone mass has been attained in the third, possibly fourth, decade of life, bone mass at any point in

TABLE 1. *Diagnostic criteria for osteoporosis*[a]

Normal	Bone mineral density (BMD) or bone mineral content (BMC) within 1 SD of young adult reference mean
Low bone mass (osteopenia)	A value for BMD or BMC between −1.0 and −2.5 SD below young adult reference mean
Osteoporosis	A value for BMD or BMC −2.5 or more SD below the young adult reference mean
Severe (established) osteoporosis	Osteoporosis with one or more fragility fractures

SD, standard deviation
[a]From Ref. 1 with permission.

time is the difference between peak adult bone mass and the loss of bone mass that has occurred since this was attained. Because age-related bone loss is a universal phenomenon in humans, any circumstance that limits an individual's ability to maximize peak adult bone mass increases the likelihood of developing osteoporosis later in life. Strategies for maximizing peak adult bone mass have been described in Chapters 46–48.

The excessive bone loss that characterizes the pathogenesis of osteoporosis results from abnormalities in the bone remodeling cycle (see Chapters 5, 25). In brief, bone remodeling is a mechanism for keeping the skeleton "young" by a process of removal of old bone and replacement with new bone. The cycle is initiated by resorption of old bone, recruitment of osteoblasts, deposition of new matrix, and mineralization of that newly deposited matrix. It appears that with each cycle there is a slight, imperceptible deficit in bone formation. The total bone loss is, therefore, a function of the number of cycles in process at any one time. Conditions that increase the rate of activation of the bone remodeling process thus increase the proportion of the skeleton undergoing remodeling at any one time and increase the rate of bone loss. In this circumstance, which is called high-turnover osteoporosis, the deficit per unit of remodeling is apparently constant. Most of the secondary causes of osteoporosis (Table 2) are associated with this increased rate of activation of the remodeling cycle. In the normal aging process, there appears to be a progressive impairment of the signaling between bone resorption and bone formation, such that with every cycle of remodeling, there is an increase in the deficit between resorption and formation because osteoblast recruitment is inefficient. Thus, excessive bone loss can occur even when activation of the skeleton is not increased and, in fact, when activation of the skeleton might be decreased. This gives rise to the concept of low- or normal-turnover osteoporosis.

CLASSIFICATION OF OSTEOPOROSIS

In addition to describing osteoporosis as being of the high- or low-turnover type, there are several other classification systems. The first is the classification into primary and secondary, the latter being osteoporosis for which a clearly identifiable etiologic mechanism is recognized. Primary osteoporosis is further characterized into postmenopausal and senile. In postmenopausal osteoporosis, there is an

TABLE 2. *Factors commonly associated with osteopenic and/or osteoporotic syndrome(s)*

Genetic
White or Asiatic ethnicity
Positive family history
Small body frame
Lifestyle
Smoking
Inactivity
Nulliparity
Excessive exercise (producing amenorrhea)
Early natural menopause
Late menarche
Nutritional factors
Milk intolerance
Life long low dietary calcium intake
Vegetarian dieting
Excessive alcohol intake
Consistently high protein intake
Medical disorders
Anorexia nervosa
Thyrotoxicosis
Hyperparathyroidism
Cushing syndrome
Type I diabetes
Alterations in gastrointestinal and hepatobiliary function
Occult osteogenesis imperfecta
Mastocytosis
Rheumatoid arthritis
"Transient" osteoporosis
Prolonged parenteral nutrition
Prolactinoma
Hemolytic anemia
Drugs
Excessive dose of thyroid hormone
Glucocorticoid drugs
Anticoagulants
Chronic lithium therapy
Chemotherapy (breast cancer or lymphoma)
Gonadotropin-releasing hormone agonist or antagonist therapy
Anticonvulsants
Chronic phosphate-binding antacid use
Extended tetracycline use[a]
Diuretics producing calciuria[a]
Phenothiazine derivatives[a]
Cyclosporin A[a]

[a]Not yet associated with decreased bone mass in humans, although identified as either toxic to bone in animals or as inducing calciuria or calcium malabsorption in humans.

apparent excess loss of cancellous bone with relative sparing of cortical bone, and the clinical syndromes involve Colles' fracture and vertebral fracture. In senile osteoporosis, there is a more concordant loss of both cortical and cancellous bone. The pathogenesis of senile osteoporosis is uncertain, but it is postulated to result from an age-related decline in renal production of 1,25-dihydroxyvitamin D and calcium malabsorption, with subsequent secondary hyperparathyroidism. It is the hyperparathyroidism that is largely responsible for the excess cortical bone loss. The fracture syndrome often seen in the patient with senile osteoporosis involves hip fracture.

CLINICAL MANIFESTATIONS OF OSTEOPOROSIS

As mentioned previously, osteoporosis without fracture is entirely without symptoms. This does not lessen its importance, because the aim of all therapies should be to prevent even the first fracture, let alone subsequent fractures. When osteoporosis is complicated by the development of an osteoporotic fracture, the symptoms and signs are those related to the fracture itself. Osteoporotic vertebral fractures may represent a unique situation, and this will be discussed separately. Primary orthopedic management of peripheral fractures should not be influenced by the fact that the fracture results from osteoporosis. Management consists of immobilization and analgesia. There does not appear to be anything about an osteoporotic fracture that results in delayed fracture union. If delayed fracture union or fracture nonunion complicates an osteoporotic fracture, one needs to look for conditions other than osteoporosis, such as osteomalacia, hyperparathyroidism, or occult forms of osteogenesis imperfecta. Immobilization should be for only a limited period of time, sufficient to ensure primary fracture healing. Longer immobilization will lead to accelerated bone loss and must be avoided. The brittleness of the osteoporotic skeleton may complicate open surgical repair of osteoporotic fractures, with limited purchase for pins, plates, screws, or nails. Restoration of the prefracture anatomic and functional state is the goal in the management of osteoporotic fractures of the appendicular skeleton. Regrettably, with respect to osteoporotic hip fractures, this is not often the outcome that is attained, given the excess morbidity and mortality already discussed. In general, this is because surgical repair of an osteoporotic hip fracture is usually a nonelective procedure. Circumstances that appear to increase mortality after a hip fracture are related to the overall medical health and nutritional status of the subject sustaining the fracture. Frail, elderly subjects taking large numbers of medications and with mental impairment have the greatest mortality, and this is particularly so in men compared with women. Of those patients who survive the early operative intervention for an osteoporotic hip fracture, less than one third are restored to their prefracture functional state, and either require institutionalized care or some form of ambulatory support.

Osteoporotic vertebral fractures are quite different from other osteoporotic fractures. Surveys of spine radiographs in older subjects suggest that many vertebral fractures have occurred in the absence of acute symptoms. If acute symptoms do occur at the time of fracture, these will be manifest as intense pain and limitation of motion. Operative intervention is infrequently required for stabilization of these fractures. However, the principles of immobilization for a short time should still hold. The concept of placing the patient with an osteoporotic fracture in a back brace for years is to be decried. Similarly, the acute skeletal pain after an osteoporotic vertebral fracture should dissipate within 4–6 weeks. If skeletal tenderness persists much beyond this, other causes for the fracture (e.g., metastatic disease, multiple myeloma) should be considered. Osteoporotic fractures of the vertebral bodies rarely result in "referred nerve pain syndrome" or long tract symptoms or signs. Again, if a fracture is complicated by these symptoms or signs, causes other than osteoporosis should be considered.

Once a vertebral body has been fractured, restoration of normal anatomy is not possible. In fact, refracture of the same vertebra with further abnormalities of shape and size is often the outcome. Thus, even those vertebral fractures that are not associated with any acute symptoms at the time of fracture give rise to chronic pain, disability, and often obvious deformity. All vertebral fractures are associated with loss of stature; in the thoracic spine this is associated with a progressive increase in the degree of kyphosis, and in the lumbar spine this is associated with a progressive flattening of the lordotic curve and scoliosis in some individuals. As the number of vertebrae involved increases and the severity of individual vertebral deformities progresses, these anatomic changes become more pronounced. There is gradual loss of the waistline contour and protuberance of the abdomen, and in severe cases the lower ribs approximate the pelvic rim and ultimately lie within the pelvis. Each of these progressive anatomic deformities is associated with symptoms. The progressive loss of stature results in progressive "shortening" of the paraspinal musculature, that is, the paraspinal muscles are actively contracting, resulting in the pain of muscle fatigue. This is the major cause of the chronic back pain in spinal osteoporosis. Careful clinical examination reveals that the skeleton (spine) itself is not tender, and most patients indicate that the pain is paraspinal. The pain is worse with prolonged standing and is often relieved by walking. After an acute fracture, there may be associated paraspinal muscle spasm, but this dissipates with time. The loss of height and the protuberant abdomen are usually not associated with direct symptoms per se, but do give the patient the emotional discomfort of the altered body image. Many patients attempt to wear abdominal flattening girdles or go on weight-reduction diets, both of which will be of limited benefit and potential harm. It is important that the patient be advised of the irreversible nature of these anatomic changes. One common complaint of patients with advanced disease is vague gastrointestinal distress aggravated by eating. This can be alleviated somewhat by having the patient consume frequent smaller meals. This is a particularly vexing problem for patients with chronic airway disease who have osteoporosis as a result of therapy with corticosteroids. In these patients, the flattened diaphragm coupled with the shortened spinal column results in marked diminution of the size of their abdominal cavity.

There are several important approaches to the long-term management of patients with these chronic deformities from spinal osteoporosis. Of particular importance is educating the patient to understand the nature of the deformity so that he or she can have realistic expectations concerning body image and the anticipated goals of therapy (relief of pain, restoration of function, maintenance of a reasonable quality of life, and prevention of further fractures). The major focus of therapy should be rehabilitation and analgesia aimed at lessening the chronic back pain. However, caution must be used with analgesics and nonsteroidal anti-inflammatory agents, many of which cause significant constipation. Straining of the stool to relieve constipation from narcotic analgesics tends to aggravate back pain substantially. In this regard, it is worth noting that many generic calcium prepara-

ions also tend to cause vague gastrointestinal symptoms, ncluding constipation in some patients. It is equally impor- ant to instruct the patient adequately in activities of daily living so that he or she bends, lifts, and stoops in a manner that does not increase strain on the brittle skeleton. Nurses, physical therapists, and occupational therapists become important partners in the management of the patient with spinal osteoporosis. In many respects, this nonpharmacologic approach to these patients is far more important than the pharmacologic therapy.

DIAGNOSTIC STUDIES IN OSTEOPOROSIS

The same diagnostic approach should be taken with patients suspected of having osteoporosis whether or not they have already sustained an osteoporotic fracture. These studies should only be undertaken once an appropriate history and physical examination have been completed. The history, physical examination, and studies should all be conducted with the aim of determining the extent and severity of disease, pathogenesis of the bone loss, and physiology of the skeleton at the time of presentation. Although postmenopausal and senile osteoporosis are the most prevalent forms of the disease, it must be remembered that as many as 20% of women who otherwise appear to have postmenopausal osteoporosis can be shown to have additional etiologic factors above and beyond their age, gender, and ethnic background. Many of these secondary causes of osteoporosis (Table 2) can be suggested from the history and physical examination so that appropriate investigations can be ordered.

If an osteoporotic fracture is suspected, it is imperative that radiographs be taken of the appropriate part of the skeleton. However, there is no clear indication for radiographs of the skeleton if fracture is not suspected. All patients suspected of having osteoporosis, with or without fracture, should have measurement of bone mass (see Chapter 23 for details). The one possible exception is the patient with far advanced disease clinically and radiographically. Because osteoporosis may be the only manifestation of many of the secondary causes listed earlier, it is appropriate to perform simple screening studies looking for these causes in each patient. A biochemical profile will provide information about renal and hepatic function, primary hyperparathyroidism, and possible malnutrition. A hematologic profile might also provide clues to the presence of myeloma and malnutrition. The precise role of hyperthyroidism, particularly exogenous, in the pathogenesis of accelerated bone loss and osteoporosis remains unresolved. Nonetheless, for the time being at least, it seems prudent to obtain a sensitive thyroid-stimulating hormone assay in all patients with documented bone loss. A 24-hour urine collection for measurement of calcium (which should always be accompanied by measurement of creatinine and sodium) will detect patients with hypercalciuria, which may be the end result of excess skeletal loss or may contribute to excess skeletal loss. In contrast, a very low urine calcium level (50 mg or less for 24 hours) may provide a clue to the presence of vitamin D malnutrition or malabsorption (2). It is our practice to obtain a 24-hour urine collection in all osteoporotic subjects. A 24-hour urine-free cortisol determination should be considered as the only test that can document occult Cushing's disease, which may have osteoporosis as the only presenting feature. The yield from using the urinary-free cortisol test is quite small, but it is probably the only way to detect this uncommon disorder. In general, the intensity with which one looks for occult secondary causes of accelerated bone loss should be related to any unusual features of the clinical presentation, such as bone loss in a premenopausal woman, in a woman very early in menopause, or in a man without obvious hypogonadism. One should also pay particular attention to patients whose fractures occur at unusual sites.

CALCITROPIC HORMONES AND BIOCHEMICAL MARKERS OF BONE REMODELING

In most cases of osteoporosis, there is no need to measure the calcitropic hormones (parathyroid hormone, calcitriol, or calcitonin) unless there is a specific indication for these measurements based on the history, physical examination, and biochemical screening. Although there are reports of abnormalities in some of these measurements when compared with published reference ranges, this is not the case when the reference values are appropriately adjusted for age, gender, and ethnic background.

In contrast, it is becoming increasingly important to monitor the biochemical markers of bone remodeling that are discussed in detail in Chapter 20. The control of bone remodeling is detailed in Chapter 5, and the role of abnormalities in the remodeling cycle in the pathogenesis of osteoporosis has been described briefly. It may be useful to make an analogy between turnover abnormalities leading to osteoporosis and abnormalities in the red cell life cycle leading to anemia. High-turnover bone loss with increased resorption and increased, but insufficient, formation would be analogous to hemolytic anemia with increased red cell destruction and increased (but insufficient) red cell formation, characterized by the increased reticulocyte count in this type of anemia. Low-turnover bone loss with normal resorption and subnormal formation would be analogous to anemia of chronic disease.

There is increasing evidence that biochemical markers of bone formation and resorption are a useful adjunct in predicting the rate of bone loss and the response to therapy. Table 3 lists the biochemical markers of bone resorption and formation that were available through commercial diagnostic laboratories at the time of this writing (December 1995). The reader should remain aware that this is a rapidly changing field and that other markers are available in laboratories of individual investigators. Table 3 also provides details of the reference intervals for these tests in healthy premenopausal white women.

Theoretically, patients with high-turnover osteoporosis should have increased levels of resorption and formation markers, should be experiencing bone loss at an accelerated rate, and should respond best to therapy with drugs that inhibit bone resorption. In contrast, those with low- or normal-turnover osteoporosis should have normal or low levels of the markers, should not be losing bone at an accelerated rate, should respond less well to antiresorptive therapy, and

TABLE 3. *Biochemical markers of bone remodeling*[a]

Marker	Reference interval[b]
Bone resorption	
Lysylpyridinoline (LP)	24–52 nM Pyd/mM Cr
Deoxylysylpyridinoline (DPD)	2.5–6.2 nM Dpd/mM Cr
N-telopeptide of the cross-links of collagen (NTX)	5–65 nM/mM creatinine based upon 95% CI
C-telopeptide of the cross-links of collagen (PICP)	13–96 nM/mM Cr
Bone formation	
Osteocalcin (OCN) [bone Gla protein (BGP)]	1.6–9.2 ng/ml
Bone specific alkaline phosphatase (BSAP)	11.6–30.6 BAP, U/L
Carboxy-terminal extension peptide of type I procollagen (PICP)	45–190 µg/L

[a]All resorption markers are based on urine collected after an overnight fast. Usually a spot sample of the first or second voided urine is analyzed. Data are normalized for creatinine excretion. All formation markers are based on random serum samples. CI, confidence interval.

[b]Reference interval is for premenopausal women.

should be treated preferentially with drugs that primarily enhance bone formation. To date, only a small fraction of these theoretical scenarios has been formally documented in prospective studies. This is mainly because the studies are not yet complete, and not necessarily because the theory is defective. The biggest difficulty has been demonstrating that the markers can be used to select therapy for individual patients, principally because the only therapies available are all antiresorptive. As therapeutic options broaden over the next several years, the usefulness of biochemical markers in this fashion will become more apparent.

At present, the most practical use of these markers is to monitor the response to therapy. It has been demonstrated that changes in markers after just 3 months of therapy are significantly related to changes in bone mass after 24 months of therapy (3). This is of considerable practical importance, particularly with respect to patient compliance with treatment, as changes in bone mass in response to therapy may not become apparent within 12 months of treatment. The markers may also provide confidence for dose adjustment, allowing the clinician to use a smaller than recommended dose of therapy if that proves sufficient to restore biochemical markers of remodeling to the normal premenopausal range.

In summary, the current approach to evaluation of the osteoporotic patient involves documentation of bone mass, documentation of fractures if present, a diligent search for secondary causes, and then an evaluation of the biochemistry of skeletal remodeling.

MEDICAL THERAPY

At the time of this writing, the only drugs approved by the Food and Drug Administration (FDA) for treatment of postmenopausal osteoporosis are estrogen, calcitonin, and the bisphosphonate alendronate. The FDA is evaluating a request for approval of a sustained-release sodium fluoride preparation. Although calcitriol and etidronate are both approved by the FDA for use in the United States, osteoporosis is currently not an approved indication. Oral calcium supplements are not subject to FDA regulation, and sodium fluoride as a supplement is also not subject to FDA regulation. In the following sections, we will discuss what is known about each of these possible therapies for postmenopausal osteoporosis.

The primary role for estrogen in the prevention of early postmenopausal bone loss and the subsequent development of osteoporotic fractures has been discussed in detail in Chapter 47. A definitive role for the use of estrogen in established osteoporosis with fractures is much less well established. Estrogen is an "antiresorptive" agent in that it inhibits bone resorption by decreasing the frequency of activation of the bone remodeling cycle. Estrogen would be expected to be most efficient if bone remodeling or bone turnover were increased. This is why it is so effective in the early stages of menopause. If an individual patient with established osteoporosis can be shown to have increased bone remodeling, estrogen will be effective in inhibiting remodeling, no matter how long it has been since the patient had her menopause. Thus, estrogen therapy will slow down the rate of bone loss in any estrogen-deficient woman so treated. However, the ability of estrogen to result in any net gain in bone mass is limited, with the best results being a 2% to 4% annual increase for 2 years. Recent studies have suggested that older women may also receive benefit from estrogen of similar magnitude (4). There are some studies showing that estrogen reduces the rate of occurrence of new vertebral fractures in patients with established osteoporosis. The usual starting dose is 0.625 mg of conjugated equine estrogen (Premarin®) or 0.05 mg of transdermal estrogen (Estraderm®). Short-term complications of estrogen therapy in women with established osteoporosis include breast tenderness and vaginal bleeding (5). If estrogens are given without progesterone, there is an increased likelihood of endometrial hyperplasia. The relationship between estrogen therapy and breast cancer is not well established, but most studies suggest that there is little, if any, increased risk of breast cancer during the first 10–15 years of therapy. Such long-term studies in established osteoporosis have not been conducted, and as long as therapy is tolerated, estrogen therapy, once indicated, should be continued indefinitely.

Synthetic salmon calcitonin (Calcimar® and Miacalcin®) is available in the United States as a subcutaneous injection or nasal spray formulation. Like estrogen, calcitonin inhibits bone resorption and slows down the rate of bone loss. The ability of calcitonin to increase bone mass is a function of the rate of bone remodeling at the time calcitonin therapy is initiated. The response is better in patients with increased bone turnover than in patients with low turnover (6). Again, a beneficial effect is observed as long as the medication is used, especially in intermittent-pulse regimens (6–11). There is increasing evidence that calcitonin has inherent analgesic properties, and many physicians recommend its use in the early postfracture period because of this effect (11). The major side effects of calcitonin are transient flushing of the face and nausea. These side effects are all dose

dependent and virtually disappear with nasal spray formulations. The recommended dose is 100 U subcutaneously daily, but few patients tolerate this large dose initially. We have found that starting with a dose as low as 25 U subcutaneously three times per week is tolerated by most patients, and the dose can be increased gradually over a period of 2–3 months if needed. Intermittent-pulse dose regimens have also been used, with documentation of increased bone mass and decreased fracture incidence (12). Calcitonin is dispensed in a concentration of 200 U/ml. Because most patients use insulin syringes calibrated for a dose of 100 U/ml, it is important that they receive adequate instruction on the amount of solution to inject to achieve the desired dosage. Therapy should be continued for as long as the drug is tolerated (12). The recommended dose of nasal spray calcitonin is 200 U daily, with limited opportunity for dose adjustment.

As discussed earlier, use of the biochemical markers may assist in finding a suitable dose of estrogen or calcitonin for individual patients, particularly if side effects or other concerns limit the recommended starting dose. For example, breast tenderness on estrogen is less likely in older women if initiated in a dose of Premarin 0.3 mg/d. If this dose can be demonstrated to have reduced the rate of resorption, dose adjustment might not be indicated. Similarly, if the markers of resorption have not changed appropriately (arbitrarily a 40% to 50% reduction from baseline after 8–12 weeks of therapy), the patient might be more willing to consider a higher dose of therapy. This is equally appropriate when trying to minimize the gastrointestinal side effects of calcitonin.

Alendronate (Fosamax®) is an amino-bisphosphonate for which extensive clinical trials have been completed worldwide; it was recently approved by the FDA for the treatment of osteoporosis. In the clinical trials, there was a progressive increase in spine and hip bone mineral density during 3 years of daily therapy at a dose of 10 mg once a day (13–15). There were fewer and less severe spinal fractures in patients receiving therapy compared with those on placebo. The drug was well tolerated with few side effects, and more than 80% of those on therapy responded with an increase in bone mass. The major potential problem with this therapy is that, in common with other bisphosphonates, oral absorption of alendronate is very poor, with less than 1% of an orally administered dose being absorbed. This poor absorption is further impaired if the medication is taken with food, any liquid except water, or with calcium supplements. These problems can be avoided if patients are advised to take the medication first thing in the morning with water and to delay breakfast for at least 30 minutes. The major side effect is esophagitis in a small proportion of patients.

Etidronate (Didronel®), the first bisphosphonate to become clinically available, has been used in several clinical trials to stabilize or increase bone mass and also to possibly reduce the vertebral fracture rate (14,16–18). However, the effect on the vertebral fracture rate is still controversial and by no means well established. The major short-term effect of bisphosphonate is nausea (14,16–18). The treatment regimen for etidronate is 400 mg orally daily for 2 weeks followed by a 10–12-week etidronate-free period, with a repeat of this 3-month cycle for 2 years. Because this bisphosphonate is poorly absorbed orally and because its absorption is obliterated when given concurrently with calcium, it is important to advise the patient not to ingest any calcium, either as a supplement or in food, for 4 hours before or after ingestion of each tablet. Clinical trials of this therapy used 1500 mg calcium as a daily supplement during the etidronate-free periods. It is imperative that etidronate be used in this rigorous treatment cycle and that the dose not be exceeded in amount or duration. There is evidence from long-term treatment of Paget's disease that large doses or longer duration of therapy with etidronate may result in a mineralization defect and an increased risk of developing osteomalacia and hip fractures. This drug is not an FDA-approved therapy for osteoporosis. As noted earlier for calcitonin and estrogen, etidronate is an antiresorptive drug. There is very little formal evidence that its effectiveness is a function of remodeling activity at the time therapy is initiated. One can anticipate a gain of 2% to 4% annually in spinal bone mass.

Although calcitriol (Rocaltrol®) in a dose of 0.25 μg/d has been shown in one study to reduce the vertebral fracture rate compared with a group of patients taking calcium alone (19), other clinical trials have not found calcitriol to be effective in this regard. However, because calcitriol is the most potent metabolite (17) of vitamin D, it does increase intestinal calcium absorption, often resulting in hypercalciuria or hypercalcemia. Patients should be cautioned to monitor their calcium intake to avoid excessive amounts and should also be monitored every 6–8 weeks for development of hypercalciuria or hypercalcemia, because clinical symptoms and signs of these conditions may be very subtle and not evident until irreversible renal damage has occurred. It is unclear what specific effect calcitriol has on bone mass, although in some instances, increments in bone mass of 1% to 2% per annum have been recorded.

The effect of calcium supplementation on bone mass and vertebral fracture rate in established osteoporotic syndromes is not well studied. Studies that are available suggest that calcium supplementation in postmenopausal women does decrease the rate of bone loss when administered in doses of 1000–1500 mg/d, especially in individuals with histories of marginally low calcium intake (5,20–24). A combination of calcium supplements and exercise has also proven effective in stabilizing skeletal bone loss rates in postmenopausal female populations. Obviously, it is important to maintain adequate calcium supplement in addition to the active drug during estrogen, calcitonin, or alendronate therapeutic interventions, because it is difficult to mineralize newly formed matrix fully in the absence of adequate calcium. However, calcium should be taken at least 1 hour after alendronate.

Sodium fluoride is widely used as a therapy for postmenopausal osteoporosis. In doses of 50–75 mg/d, the increase in spinal bone mass achieved with sodium fluoride approximates 8% per year, twice that seen with either estrogen, calcitonin, or bisphosphonates. However, there is little evidence from properly conducted clinical trials that this increase in bone mass translates into a reduction in vertebral fractures. Moreover, sodium fluoride is associated with a significant degree of gastrointestinal distress and also a painful lower-extremity syndrome believed to represent stress fractures induced by fluoride. Recently reported stud-

ies with a lower dose of a slow-release sodium fluoride preparation administered cyclically have indicated a beneficial effect on vertebral fracture rates (25). The best results were reported in those osteoporotic patients with the highest bone mass (>65% of peak adult bone mass). Therapy was most effective in preventing fractures in previously nonfractured vertebrae; there was no significant effect on the progression of fractures in vertebra that were already fractured before initiation of treatment. It should be emphasized that these patients were also subjected to estrogen therapy. An FDA advisory panel recently recommended that a slow-release sodium fluoride preparation be approved for treatment of osteoporosis (26).

There are reports that the prevalence of osteoporotic hip fractures decreases in hypertensive patients receiving long-term therapy with hydrochlorothiazide (13,16,18). This has not been confirmed in all studies. To our knowledge, there are no formal prospective studies of thiazide diuretic therapy in osteoporotic or postmenopausal normotensive populations. Until such studies are reported and shown to be effective, thiazide diuretics should not be used as therapy for osteoporosis. However, a case could be made for selecting thiazides as the diuretic of choice in patients with osteoporosis, should diuretic therapy be otherwise indicated. Because thiazides decrease renal excretion of calcium and, uncommonly, may lead to mild hypercalcemia, extreme caution should be used when considering calcitriol therapy in a patient taking thiazides, or thiazide therapy in a patient taking calcitriol. Side effects such as hypomagnesemia, hyperglycemia, hypercholesterolemia, and hypokalemia preclude advocating this drug as potentially therapeutic for osteoporotic patients who are not hypertensive (27,28).

Newer generations of bisphosphonates, synthetic parathyroid hormone, selective estrogen receptor modulators (SERMs), and various combinations and treatment regimens of these experimental drugs, as well as the drugs listed earlier, are currently undergoing extensive clinical trials. At present, the safety and efficacy of these various drugs and their potential combinations are not well established. Consequently, their use cannot be recommended. One exception is the antiestrogen tamoxifen. This drug is widely prescribed for women with breast cancer to minimize the likelihood of recurrence. Tamoxifen inhibits bone resorption in the same manner as estrogen and is effective in preserving bone mass. However, because of reported side effects, not the least of which is endometrial carcinoma, its use should be restricted to women for whom it is prescribed as adjunctive therapy for breast cancer. Table 4 lists the several therapies that are currently under active investigation in the United States. It is anticipated that some of these therapies will become available for clinical use by the year 2000.

TABLE 4. *Pharmacologic therapies for osteoporosis*

Approved by the FDA with an osteoporosis indication
Estrogen
Calcitonin, subcutaneous or nasal spray
Alendronate
Approved by the FDA without an osteoporosis indication
Calcitriol
Etidronate
Thiazide
Approval pending for an osteoporosis indication
Sodium fluoride, slow-release
In clinical trial
I. SERM
Droloxifene
Roloxifene
II. Bisphosphonate
Ibandronate
Risedronate
Tiludronate
III. Parathyroid hormone

FDA, Food and Drug Administration; SERM, selective estrogen receptor modulator.

SELECTING A THERAPY AND MONITORING THE RESPONSE TO THERAPY

At a minimum, every patient with established osteoporosis, with or without fractures, should be given supplemental calcium at 1000–1500 mg/d. Specific therapy for osteoporosis should be restricted to estrogen, calcitonin, and alendronate, given that these drugs are approved by the FDA for an osteoporosis indication. Bone mass, which should always be measured at baseline, should be monitored at the end of 12 months of therapy. A decrease in bone mass of 2% or greater should prompt a change in therapy—either a change in dose or a change in medication. After a patient has experienced 1 full year of successful therapy, that is, 1 year of therapy with either an increase in bone mass or a 2% decrease, monitoring can be restricted to biannual measurement of bone mass. At present, there is no indication that therapy should be discontinued as long as the patient is tolerating the medication and there is no progressive decrement in bone mass. It should be noted that the antifracture efficacy of each of these drugs during the early therapeutic phase is not well established, and the occurrence of an osteoporotic fracture within the first 6–12 months of therapy should not be taken as an indication of failed therapy. The patient should be made completely aware of this before initiation of therapy. We recommend that each patient have a baseline measurement of biochemical markers of bone remodeling before initiating therapy. The patient should be seen and clinically evaluated 6–8 weeks later to ascertain compliance and possible side effects from therapy. It would also be appropriate to repeat the biochemistry at this time to determine that there is indeed a decrease in the rate of bone remodeling. If there is no satisfactory change in the biochemistry, one should consider increasing the dose. If the dose of medication is changed for whatever reason, clinical and biochemical evaluation should be repeated in 6–8 weeks until a satisfactory response is achieved. If there is no response to 3 months of therapy, one should consider a change in medication. Studies confirming the scientific rationale for monitoring biochemical markers of bone remodeling have not been fully completed. However, available data suggest that the anticipated early (3 months or less) change in several of the markers, in response to successful therapy, is greater than the precision error of the biochemical measurement. This is in contrast to serial measure-

ment of bone mineral density, for which even a good response to therapy cannot be detected within 1 year in most patients because the anticipated change is close to the precision limits of the methods. Furthermore, there is evidence that early (3 months) changes in biochemical markers reliably predict later (24 months) changes in bone mass. Most patients and their treating physicians are reluctant to take therapy for 12 months before measurable feedback is available, and this practical consideration may dictate the frequency with which biochemical markers are monitored. As far as is known, there are no ill effects of long-term use of calcitonin or alendronate in the treatment schedules described previously. Cost and convenience become important factors in long-term patient acceptance of these drugs. Because of the potential association between long-term estrogen therapy and development of endometrial and breast cancer, appropriate monitoring for these complications must be continued. Patients must be instructed in the technique of monthly breast self-examination and must undergo an annual examination by a clinician and an annual mammogram. All episodes of unexplained vaginal bleeding must be fully evaluated by a gynecologist. In women with an intact uterus, progesterone should be given along with estrogen; most patients will soon develop either amenorrhea or a stable, recognizable bleeding pattern, which should not give rise to concern or investigation.

It is important to reemphasize that drug therapy should never be substituted for the common-sense approaches to daily living discussed in some detail in earlier sections. This includes emphasizing safety and fall prevention and avoiding drugs such as sedatives, hypnotics, and antihypertensives, which might predispose to sedation, ataxia, or postural hypotension. Patients should all be encouraged to become involved in a regular active exercise/rehabilitation program. With appropriate medical, nursing, and rehabilitation care, most patients, except for those with the most advanced disease with multiple vertebral compression fractures, can be expected to be restored to reasonable functional health with a good quality of life. Likewise, an anticipated goal of therapy should be to prevent even the first osteoporotic fracture in patients whose therapy is initiated early.

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JOURNAL OF BONE AND MINERAL RESEARCH
Volume 17, Number 1, 2002

Editorial

Bone Turnover Matters: The Raloxifene Treatment Paradox of Dramatic Decreases in Vertebral Fractures Without Commensurate Increases in Bone Density

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The summum bonum of osteoporosis treatment is the prevention of new fractures. In vitro studies have shown that 60–80% of the compressive strength of bone is caused by its mineral content.[1] Correspondingly, observational studies show that baseline bone mineral density (BMD) measurements at multiple skeletal sites can predict various types of osteoporotic fractures in postmenopausal women.[2] In general, a decrease in BMD of 1.0 SD increases the risk of future fractures by ~2.0-fold. The observational data from epidemiological studies have been confirmed by results of randomized clinical trials (RCTs) showing that antiresorptive agents both increase BMD and decrease vertebral fractures.[3] These considerations have led to the widespread belief that changes in BMD can serve as a surrogate for assessing treatment effects on fracture risk. Based mainly on the failure of large increases in BMD induced by sodium fluoride therapy to reduce fracture risk,[4] the U.S. Food and Drug Administration has not allowed surrogate markers for fractures such as BMD to be used as primary endpoints for assessing efficacy of antiosteoporosis drugs. However, sodium fluoride therapy alters bone crystalline structure and reduces bone strength,[5] so these results cannot be generalized to other treatments.

Raloxifene is a selective estrogen receptor modulator (SERM) with a spectrum of tissue-specific agonist-antagonist effects on estrogen target tissues but that acts on bone as an estrogen agonist.[6] In the large MORE trial of 7705 women with osteoporosis,[7] 3 years of raloxifene treatment in dosages of 30 mg/day or 60 mg/day increased BMD at the lumbar spine by 2.6% and 2.7%, respectively, and at the femoral neck by 2.1% and 2.4%, respectively, as compared with placebo. These modest increases in BMD were associated with large decreases in vertebral fractures of 38% and 41% for the two dosages, respectively. Similarly, in the PROOF trial, treatment with nasal spray calcitonin increased lumbar spine BMD by only 1.2% but decreased vertebral fracture risk by 36%.[8] However, neither raloxifene[7] nor nasal spray calcitonin[8] treatment reduced the risk for hip and other nonvertebral fractures. By contrast, the more potent antiresorptive agents estrogen,[9] alendronate,[10] and risedronate[11] increased lumbar spine BMD over 1–3 years by 5.3–8.8%, but RCTs with these agents have resulted in reductions in the vertebral fracture rate of about 40–50% (reviewed by Faulkner[12]), only slightly more than were achieved with raloxifene or calcitonin therapy.

In this issue of the *Journal*, Sarkar et al.[13] report on an extensive statistical reanalysis of the MORE data to assess further the relationship between changes in BMD and changes in vertebral fracture risk. Using logistic regression models with the two dosages of raloxifene pooled, they find that fracture risk varied inversely with baseline BMD values but that the decrease in vertebral fracture risk was similar across the range of increases in femoral neck or lumbar spine BMD and that only a small fraction of the observed reduction in vertebral fracture risk with raloxifene therapy could be accounted for by the increase in lumbar spine BMD. The authors conclude that antiresorptive agents that induce greater increases in BMD cannot necessarily be assumed more efficacious in reducing fracture risk than those that elicit lesser increases. However, the article leaves unresolved the reason for discrepancy between the small

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increases in BMD and the relatively large decreases in vertebral fracture risk with raloxifene therapy.

Thus, there are two paradoxes that require explanation. First, how can the modest increase in BMD induced by raloxifene or nasal spray calcitonin therapy decrease fracture risk by almost the same extent as more potent antiresorptive agents that increase BMD by a 2- to 3-fold greater extent? Second, this paradox is subsumed into an even larger paradox: Why do the small increases in BMD observed after antiresorptive therapy result in a much larger decrease in vertebral fracture rate than predicted from the relationship between BMD and vertebral fracture risk found in observational studies? We will examine the second paradox first.

In 1996,[14] we advanced the hypothesis that antiresorptive agents were able to reduce vertebral fracture rates substantially without inducing large increases in BMD because of their ability to normalize high bone turnover in patients with osteoporosis. We further suggested that high bone turnover contributes substantially to vertebral fracture risk because of its disruptive effect on the microarchitecture of cancellous bone. Using histomorphometry, Parfitt et al.[15] have shown that increased osteoclastic activity associated with high bone turnover in postmenopausal women leads to perforative resorption of cancellous plates, loss of trabeculae, and trabecular discontinuity. Because much of the strength of cancellous bone is caused by its microarchitecture, the loss of trabecular connectivity and other adverse structural consequences of increased osteoclastic activity clearly could predispose to fractures of the vertebrae and other skeletal sites that have a high content of cancellous bone.

Our hypothesis was based on a reanalysis[14] of a 1-year RCT of transdermal estrogen and placebo therapy of postmenopausal women with osteoporosis[9] using computer generated, three-dimensional graphic plots that related the observed vertebral fracture rate to lumbar spine BMD and to bone turnover assessed directly by tetracycline-based histomorphometry of iliac biopsy samples. As shown in Fig. 1A, placebo-treated women with osteoporosis from this RCT had two vertebral fracture peaks, a somewhat higher peak that was associated with high bone turnover and a somewhat lower one that was associated with low baseline lumbar spine BMD. However, in the estrogen-treated women (Fig. 1B), the fracture peak associated with high turnover was not present whereas the fracture peak associated with low BMD was maintained, presumably because the increases in BMD induced by treatment were modest. Although these data plots are only semiquantitative, Fig. 1B suggests that more than one-half of the incident vertebral fractures in untreated postmenopausal osteoporotic women may be caused by high bone turnover and the remainder are caused by low BMD. Figure 1B further suggests that the short-term reduction in vertebral fractures induced by estrogen therapy is caused by mainly elimination of the fracture peak associated with high bone turnover. Because the average reduction in vertebral fracture risk produced by effective antiresorptive agents also is about 50%,[12] it is likely that the same mechanism is occurring in them as well. Moreover, the hypothesis that antiresorptive agents reduce fracture risk

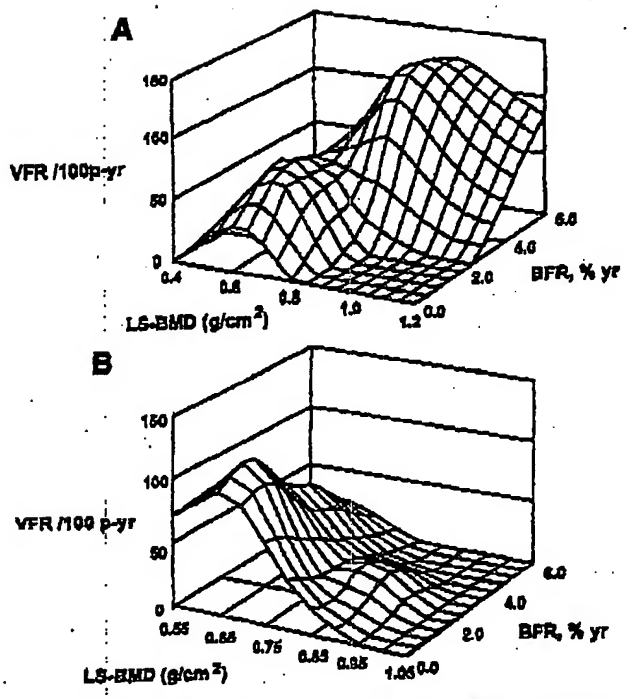

FIG. 1. Computer generated, three-dimensional surface plot of data from a 1-year RCT in postmenopausal women with osteoporosis reported by Lufkin et al.[9] comparing results in (A) placebo-treatment and (B) treatment with transdermal estrogen. The two plots show the relationship among vertebral fracture rate (VFR), lumbar spine BMD (LS-BMD), and bone formation rate (BFR) assessed by double tetracycline labeling of an iliac biopsy sample. Note that there are two fracture peaks in the placebo-treatment limb, one associated with high bone turnover and one associated with low BMD. By contrast, in the estrogen-treatment limb, the fracture peak associated with high bone turnover has been eliminated whereas the fracture peak associated with the low BMD is still present. Reprinted from Riggs BL, Melton LJ III, O'Fallon WM 1996 Drug therapy for vertebral fractures in osteoporosis: Evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. Bone 18(Suppl):197S–201S, Figure 2, with permission from Elsevier Science.

mainly by reducing bone turnover is supported by prospective studies[16,17] showing that the baseline level of bone turnover markers can predict fracture risk independently of BMD. Finally, the hypothesis explains why less potent antiresorptive drugs such as raloxifene[7] and calcitonin[8] can reduce substantially vertebral fracture risk but not hip fracture risk whereas alendronate[18] and risedronate[11,19] can reduce both vertebral and hip fracture risk. High bone turnover does weaken cortical bone by increasing its porosity, but, usually, it does not produce major microarchitectural disruption. Thus, both a decrease in bone turnover and an increase in hip BMD may be required to decrease hip fracture risk.

More recently, Faulkner[12] also addressed the paradox of why small increases in BMD can result in dramatic decreases in vertebral fracture rates. However, he dismisses as unlikely that decreases in bone turnover induced by antire-

sorptive agents reduce fracture risk independently of their effect on increasing BMD. Instead, he concludes that "bone matters"; that is, the treatment-induced increases in BMD are the cause of the decreased fracture rate induced by antiresorptive agents. He suggests that the paradox can be explained by (1) technical limitations of measuring BMD that result in an underestimation of treatment-induced increases in cancellous bone, (2) differences in the skeletal fragility among study populations, and (3) that the BMD/fracture relationship may not be bidirectional. He also acknowledges the possibility of nondensity-related effects of therapeutics on vision, coordination, muscle strength, and other fall-related factors. However, this possibility is not supported by recent reports that bisphosphonate treatment reduces fractures when BMD is low but not when it is above the threshold for osteoporosis.[18,19]

Although our 1996 hypothesis and that of Faulkner may not be mutually exclusive, we believe that "bone turnover matters" and that the normalization of high bone turnover is by far the major cause of the discrepant BMD/fracture risk relationship after antiresorptive therapy. Nonetheless, neither we nor Faulkner have explained adequately the first paradox: Why does treatment of osteoporotic patients with raloxifene and calcitonin, which induce only minimal increases in BMD, reduce vertebral fracture risk almost as much as the more potent antiresorptive agents, which induce much larger BMD increases? Thus, we believe that a modification of our 1996 hypothesis is required.

We now suggest that elimination of the disruptive effect of perforative resorption on the microarchitecture of cancellous bone can be achieved by a relatively small effective dosage of an antiresorptive agent but that a larger effective dosage is required to increase BMD further. Thus, both less potent antiresorptive drugs such as raloxifene or calcitonin and more potent ones such as estrogen or bisphosphonates will reduce vertebral fracture risk by an almost comparable degree because it is only necessary to reach a low therapeutic threshold to reduce perforative resorption. However, a greater effective dosage is required to produce larger increases in BMD, which can be achieved using the more potent antiresorptive agents but not the less potent ones. These further increases in BMD confer an additional decrease in fracture risk beyond that achieved by reducing bone turnover, but this decrease is relatively small. Indeed, Sarkar et al.[13] estimated the contribution of increases in BMD to vertebral fracture reduction is 4% for raloxifene therapy whereas Cummings et al.[20] estimated that it is 17% for alendronate therapy. Thus, for substantial BMD-based reductions in vertebral fracture risk to occur, relatively large increases in BMD will be required. Moreover, although population-based studies predict that increasing BMD by 1 SD will reduce fracture risk by one-half; this is unlikely to occur in the treatment of patients with osteoporosis because increases in BMD will not restore the bone microarchitecture that has been disrupted during the process of bone loss. Also, results from many RCTs have shown that even the most potent antiresorptive agents are unlikely to increase BMD by more than 1 SD (10–13%). Thus, the large increases necessary for a substantial BMD-based reduction in fracture risk will require treatment with formation-stimulating agents, such as parathyroid hormone.[21]

Although this modified hypothesis is plausible and seems to agree with observed data better than do conventional concepts, it needs experimental confirmation. This will be difficult to accomplish at present because of the limitations in current technology, but new instrumentation may make testing possible in the near future. Preliminary studies using a prototype instrument for high sensitivity, peripheral three-dimensional quantitative computed tomography, have shown that it is feasible to quantify the degree of microarchitectural disruption of cancellous bone, and the same instrument can make independent measurements of changes in cancellous and cortical BMD.[22] Thus, using this new technology, a head-to-head comparison of a less potent with a more potent antiresorptive agent should soon allow for a rigorous test of this hypothesis.

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EVIDENCE-BASED MEDICINE AND OSTEOPOROSIS: A COMPARISON OF FRACTURE RISK REDUCTION DATA FROM OSTEOPOROSIS RANDOMISED CLINICAL TRIALS

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SUMMARY The goal of osteoporosis therapy is to prevent fractures, and many therapies are available for this disease. Regarding proven fracture benefit, however, the quality of the randomised clinical trial evidence varies substantially among therapies. The purpose of this paper is, therefore, to review the published osteoporosis randomised clinical trial literature and to assess the quality of the evidence. Although more than 35 randomised trials for different therapies were reviewed, only alendronate and vitamin D plus calcium have clearly demonstrated a fracture benefit, with alendronate providing the greatest relative risk reduction. Quality clinical trial fracture data for calcitonin, etidronate, fluoride, hormone replacement therapy, parathyroid hormone, calcitriol (and other vitamin D preparations), vitamin D and calcium monotherapy, and selective oestrogen receptor modulators are either lacking or inconclusive or published only as abstracts. (*Int J Clin Pract* 1999; 53(2): 122-129)

Osteoporosis, a disease characterised by low bone mass and deterioration of bone architecture, leads to increased susceptibility to fractures and is therefore a significant public health problem.[1,2] A greater understanding of the pathophysiology of osteoporosis has led to the development of numerous treatments including hormone replacement therapy (HRT), calcium, vitamin D, bisphosphonates, fluoride salts, calcitonin, calcitriol, parathyroid hormone and new selective oestrogen receptor modulators.[3-11] Although many therapies have demonstrated some ability to impact serum biochemical markers of osteoporosis (e.g. alkaline phosphatase) and/or decrease the rate of loss of bone mineral density (BMD), the ultimate goal of osteoporosis therapy is to prevent fractures. With regard to proven fracture benefit, the quality of the clinical trial evidence varies substantially among therapies, and today's health-care practitioner is faced with a challenging task in selecting the best treatment for his or her patients.

For those osteoporosis therapies for which randomised clinical trial fracture data exist, there can be study design and analysis issues that affect the interpretation of the evidence regarding fracture prevention. Firstly, fracture should be the primary endpoint of a clinical trial in which we draw any conclusion about fracture efficacy. There is always the possibility with post-hoc analysis that a positive, statistically significant treatment effect may be found by chance alone, especially in randomised clinical trials with small sample sizes. Second, all randomised clinical trials should be appropriately blinded; if at least a double-blind is not employed, there is a possibility that an observed treatment effect is due to patient and/or investigator bias. And finally, patients with fracture, as opposed to fracture rates (i.e. number of fractures per sum of observation times) should be reported and used to compute the relative risk and level of statistical significance. Reporting fracture rates instead of patients with fracture and basing statistical analyses upon them has been criticised by Windeler and Lange.[19] Using event rates instead of patients with events violates basic statistical assumptions and invalidates the use of common statistical tests and estimators. The most important assumption violated is that the occurrence of one event does not increase the likelihood of a subsequent event; for osteoporosis this is not true – once a fracture occurs the risk for a subsequent fracture increases.[20,21]

Because these randomised clinical trial design and analysis shortcomings may exist, and because osteoporosis is a serious public health concern, it would be extremely useful and practical to review the osteoporosis clinical trial literature and to evaluate trial results based upon the quality of the evidence on fracture prevention.

OBJECTIVE

The objective of this paper is to review the osteoporosis treatment randomised clinical trial literature and to look specifically at fracture risk reduction. It is important here to define treatment. It has been suggested that, both conceptually and practically, it is useful to separate osteoporosis management into primary prevention and secondary intervention (also known as treatment).[22] Generally, prevention is defined as therapy for women with normal bone mass (administered with the intent of preserving bone mass and preventing first fracture), and treatment is defined as therapy for women with low BMD and/or with prior fracture (administered with the intent of restoring bone strength and preventing further fractures). Randomised clinical trials with fracture endpoints

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have to date been conducted only in treatment populations, so this paper addresses treatment.

The review focuses on the clinical outcome of fracture. Although BMD has been demonstrated to be a good predictor of future fracture risk,[23-26] it is nonetheless a surrogate measure of efficacy in clinical trials. Kanis *et al*[27] have discussed some of the limitations of BMD measurement and note, among other issues, that such measurement does not capture all the determinants of skeletal fragility including the rate of bone turnover, its plasticity and the continuity of trabecular structures in cancellous bone.

METHODOLOGY

A literature search was issued on Medline (through October 1998) for published articles in the English language on osteoporosis randomised clinical trials that had examined the impact of treatment on fracture risk. The reference section of these papers was searched for other relevant articles. Each of the articles was then reviewed to assess the reported relative risk for fracture (treatment *vs* control) and the 95% confidence interval (95% CI) or p-value. Certainly one of the concerns of comparing the efficacy of different interventions from different randomised clinical trials is the possibility that the relative risk with intervention is not constant across risk strata. If this is the case, comparing relative risks across randomised clinical trials is inappropriate, unless all the studies have the exact same baseline risk, which is unlikely. Whether the relative risk reduction is constant or not will vary by endpoint and/or disease state.[28-30] In osteoporosis, however, there is evidence that the relative risk reduction for fracture, for any given therapy, is constant across risk strata. A recent analysis of randomised clinical trial fracture data suggests that the relative fracture risk reduction is comparable for: (a) women aged <75 and women aged ≥75, (b) women with femoral neck BMD <0.59 g/cm² and women with femoral neck BMD ≥0.59 g/cm², (c) women with one versus women with ≥2 existing vertebral fractures and (d) women with and women without a history of postmenopausal fracture.[31] Because of this finding, the relative risk is an adequate means for comparing the efficacy of osteoporosis interventions assessed in different randomised clinical trials.

Criteria for fracture evidence

The quality of the evidence for fracture prevention in the randomised clinical trial literature was evaluated with five key criteria, all of which had to be met if in fact an agent had conclusively demonstrated fracture benefit. First, fracture must be a primary endpoint of the study. If a paper reported fracture as a secondary endpoint, it was discussed, but fracture benefit was then not considered conclusive even if all other criteria were met. Second, patients and investigators must be blinded to treatment assignment. If this was unclear, the paper was still discussed; however, results from clearly open-label randomised clinical trials were not considered valid. Third, the relative risk and statistical significance must be computed using the patients with fracture method as opposed to the fracture rate method. If the relative risk and statistical significance was computed using the fracture rate method by the original authors and their findings were reported to be statistically significant, the relative risk and p-value were recomputed using the patient with fracture method (this could be done only if there were enough data provided in the paper to do so). The p-value is estimated using the chi-square test statistic (see below). Fourth, if several randomised clinical trials have been conducted on the same agent, consistent results should be reported for that agent. And fifth, the study results on fractures should be published in a peer-reviewed journal. If interim study results for a particular intervention had been published as an abstract, they were discussed, but this did not meet the fifth criterion.

If the authors of the original paper recommended caution in interpreting the results (e.g. because of a small sample size), this recommendation was heeded. Also, if a particular clinical trial found drug-related adverse events to be significantly increased for patients who were administered the study drug, this was discussed; otherwise readers can assume that the safety and tolerability in any clinical trial were comparable between treatment and control groups.

Statistics

If the results of a particular study were re-examined in this review, the relative risk and p-value were estimated using a chi-square test statistic (not enough data were provided in any paper to conduct more sophisticated analyses such as the log-rank test). A chi-square of 3.84 with one degree of freedom corresponds to a p-value of 0.05, and in this review any chi-square value less than this critical value was considered non-significant. The Yates continuity correction for chi-square is somewhat controversial but is usually recommended when the expected frequency in any of the cells in a 2 x 2 table is less than 5. When the expected counts are small, the sampling distribution of chi-square for that analysis may depart substantially from normal.[32] The Yates corrected chi-square is more conservative than the unadjusted chi-square and will result in a lower chi-square and thus a higher p-value. Therefore the Yates correction was used only if, in a reanalysis, at least one cell in the 2 x 2 table had an expected value of 5 or less and the unadjusted chi-square was ≥3.84 (i.e. $p \leq 0.05$).

It should be stated that if the results of any reanalysis in this review paper differ from those presented by the original authors, it does not imply that those authors were intentionally misleading. All it suggests is that with the information available in the original paper and with the statistical tests used here, there may be other ways of interpreting the data and that this should be considered by the physician.

RESULTS

Although over 35 randomised clinical trials were found in the search that reported fracture data, only two trials, a three-year study of the bisphosphonate alendronate[12] and a three-year study of vitamin D plus calcium[11] satisfactorily

Table 1. Osteoporosis interventions with demonstrated fracture benefit

Citation and study drug/ control	Study info	Key results (relative risk*, 95% CI, patients with events, treatment vs control)
Black *et al*[12] Alendronate 10 mg + vitamin D and calcium *versus* Placebo + vitamin D and calcium	• n=2027 • Follow-up 3 yrs • Mean age 71 • Low bone mass + previous vertebral fracture • Vitamin D and calcium replete population • Community dwelling	*Hip fracture*: 0.49 (0.23-0.99); 11 treatment, 22 control *Vertebral fracture*: Radiographic: 0.53 (0.41-0.68); 78 treatment, 145 control Clinical: 0.45 (0.27-0.72); 23 treatment, 50 control *Wrist fracture*: 0.52 (0.31-0.87); 22 treatment, 41 control
Chapuy et al[11] 20 mg (800 IU) vitamin D_3 + 1.2 g tricalcium phosphate *versus* Double placebo	• n=3270 • Follow-up 3 yrs • Mean age 84 • Bone mass and previous fracture unspecified • Calcium and vitamin D insufficiency • Nursing home	*Hip fracture*: 0.73 (0.62-0.84); 137 treament, 178 control *Non-vertebral fracture*: 0.72 (0.60-0.84); 255 treatment, 308 control

*relative hazard is presented instead of relative risk; CI confidence interval

met all five criteria for clearly demonstrating a fracture benefit (Table 1). Both agents have demonstrated an ability to reduce the risk of hip fracture, but the relative risk reduction for hip fracture was approximately two times greater with alendronate (51% for alendronate *vs* 27% for vitamin D plus calcium). Of the two, only alendronate has demonstrated an ability to reduce the risk of spine fractures as well.

For alendronate, there was additional evidence from an earlier randomised clinical trial by Liberman *et al*[13] that the bisphosphonate reduced the relative risk of women having a spine fracture by 48% (p=0.03) over three years, which is consistent with the data reported by Black *et al*.[12] The Liberman study results were not included in Table 1 because fracture was a predefined secondary endpoint of the study.

A randomised clinical trial by Chapuy *et al*[11] in 1992 reported the hip fracture risk reduction observed with vitamin D plus calcium over a course of 18 months in a non-ambulatory nursing home bound population, but the 36-month follow-up of the same population that was reported, again by Chapuy *et al*,[11] in 1994 was used for this review (Table 1). Another randomised clinical trial of vitamin D plus calcium by Dawson-Hughes *et al*[14] found that three years of treatment with vitamin D plus calcium reduced the relative risk of any non-spine fracture in non-institutionalised men and women age 65 and older by 50% (RR=0.50; p=0.02). Although the authors suggested the fracture results should be interpreted with some caution because of the relatively small sample size of the study (n=389), the findings do appear to support the data reported by Chapuy *et al*.[11] The populations in Chapuy *et al*[11] and Dawson-Hughes *et al*[14] both had a low dietary intake of calcium (in the alendronate study, both treatment and control groups received vitamin D plus calcium, while in the vitamin D plus calcium studies, the control groups received only double-placebo); the effect of vitamin D plus calcium on a vitamin D/calcium replete population has not been studied, so is unknown.

Vitamin D monotherapy and calcium monotherapy

The effect of vitamin D or calcium alone on fracture risk is uncertain. For calcium monotherapy, three studies have reported a statistically significant decrease in fracture risk.[15-17] In a four-year trial (n=86) by Reid *et al*,[15] the authors reported a significant reduction in the rate of symptomatic fractures (log-rank statistic, chi-square=4.35, p=0.037). In another study, only fracture rate data were reported by Chevalley *et al*,[16] so the relative risk and statistical significance using the patient with fracture method could not be computed for the 18-month study (n=156). Using the patient with fracture method, Recker *et al*[17] did find that over the course of four years, calcium significantly reduced (p=0.023) the risk of spine fracture in patients with prevalent fracture at baseline (n=94). No effect was found by Recker *et al*[17] in patients without fracture at baseline (n=103). With regard to vitamin D monotherapy, Lips *et al*[18] found no impact on hip or peripheral fracture risk in a large 3.5 year trial of 2578 men and women aged 70 and older.

Hormone replacement therapy

For HRT, most of the evidence on fracture benefit comes from retrospective studies; there is no prospective randomised clinical trial evidence that such therapy reduces the risk of fracture. In a one-year randomised trial, Lufkin *et al*[5] reported a relative risk reduction of 61% (RR=0.39; p=0.04) for radiographic vertebral fractures for women administered HRT (n=75). The authors made their calculation of the relative risk and statistical significance using fracture rate data. If patients with fracture are used instead to compute the relative risk and statistical significance, of 68 women with repeat radiographs available after one year, 7 of 34 women (21%) in the treatment group and 12 of 34 (35%) women in the control group suffered a spine fracture, and the relative risk is not statistically significant (RR=0.58, chi-square=1.83, p>0.17). No beneficial effect on fracture risk (or cardiovascular disease risk) was found for HRT in the recent Heart and Estrogen/progestin Replacement Study,[19] but the large four-year randomised clinical trial (n=2763) included fracture only as a secondary endpoint and had inadequate statistical power to examine the impact of intervention on fracture incidence.

Etidronate and other bisphosponates

Etidronate is another bisphosphonate commonly used to treat osteoporosis. However, prospective evidence of fracture prevention meeting the five criteria was not found for this agent. In a two-year randomised clinical trial (n=429) by Watts *et al*,[8] the authors reported a significant reduction (p=0.044) in the relative risk of spine fracture for the entire

study population as well as a significant reduction (p=0.006) in the relative risk of spine fracture for a high risk subgroup (defined as subjects below the 50th percentile for the baseline values of BMD) using the appropriate patient with fracture method. Harris *et al*[8] reported on the same study population with blinded treatment carried out for one additional year. They found that etidronate significantly reduced (p<0.05) the radiographic vertebral fracture rate in patients at higher risk for fracture (defined as subjects below the 50th percentile for values of BMD and ≥3 vertebral fractures at baseline). Not enough information was provided by Harris *et al* to compute the relative risk and significance for this highest risk subgroup using the patients with fracture method. For the entire study population, however, 32 of 184 women (17.4%) on no etidronate and 28 of 196 women (14.3%) on etidronate suffered a spine fracture;[8] the relative risk is not statistically significant (RR=0.82, chi-square=0.69, p>0.40). Thus, when looking at the entire study population, there was a significant reduction in vertebral fracture risk with two years of etidronate therapy, but not with three years. When examining women with low bone mass and prior fractures, the first two years with etidronate therapy resulted in a significant fracture risk reduction, but we cannot draw any conclusions about the third year for this high risk subgroup.

There was also a three-year randomised clinical trial (n=66) by Storm *et al*[9] that reported a significant reduction (p=0.023) in the vertebral fracture rate for women administered etidronate (from weeks 60 to 150), but there were not enough data presented in the paper to compute the relative risk and statistical significance using the patient with fracture method.

Finally, in a four-year randomised clinical trial (n=72) of HRT plus etidronate by Wimalawansa,[40] the author reported fracture rates as a secondary endpoint and there were no significant differences between groups, even with the fracture rate method.

There was one randomised clinical trial (n=48) for another bisphosphonate, pamidronate, but the fracture rate was a secondary endpoint.[41] Even with the fracture rate method there was no significant effect on fracture risk after two years of follow-up.

Calcitriol (1,25 dihydroxyvitamin D_3) and other vitamin D preparations

A three-year randomised clinical trial of calcitriol versus calcium in 622 postmenopausal women by Tilyard *et al*[5] found the rates of vertebral and peripheral fractures were significantly lower in those treated with calcitriol, but the study was only single blinded, so there was a greater than usual potential for bias.[42] Other randomised clinical trials of calcitriol have demonstrated no impact of treatment on vertebral fracture risk.[43-45] A randomised clinical trial (n=62) by Gallagher and Riggs[46] reported a significant decrease in the vertebral fracture rate after one year of therapy with calcitriol, but because the number of patients with fracture was not reported, the relative risk and statistical significance could not be computed using the patients with fracture method. A one-year randomised clinical trial (n=80) by Orimo *et al*[47] reported a significant reduction (p=0.029) in the vertebral fracture rate with 1α hydroxyvitamin D_3. However, when the results were reanalysed using the patient with fracture method, for 53 women with X-ray analyses, two of 25 women (8%) in the treatment group and seven of 28 women (25%) in the control group suffered a spine fracture, and the difference between treatment and control was not statistically significant (RR=0.32, chi-square=2.71, p=0.10). Finally, another randomised clinical trial (n=113) of 1α hydroxyvitamin D_3 by Shiraki *et al*[48] found no significant effect on vertebral fracture risk after two years of therapy, even when using the fracture rate method.

Fluoride

In randomised clinical trials by Pak *et al*[6] (n=110) and Reginster *et al*[49] (n=200), a significant reduction in vertebral fractures with fluoride plus calcium using the patient with fracture method was reported over the course of four years, but overall in the literature the clinical trial results for fluoride have been inconsistent[4,49-54] and often only fracture rates have been reported. A recent study (n=354) by Meunier *et al*[54] found that over two years, fluoride added to vitamin D plus calcium was no more effective in preventing spine and peripheral fractures than vitamin D plus calcium alone. In a four-year randomised clinical trial (n=202) by Riggs *et al*,[50] the authors found no effect of fluoride therapy on vertebral fracture risk, but they did find a significant increase in the risk of non-vertebral, non-stress fractures (own computation, patient with fracture method: RR=1.59, chi-square=4.13, p<0.05). In the discussion, Riggs *et al* noted that fluoride treatment increases cancellous bone mass but decreases cortical bone mass and increases skeletal fragility.

Riggs *et al*[50] reported an increased risk of side-effects (gastrointestinal discomfort and lower extremity pain) for patients administered fluoride therapy. Meunier *et al*[54] also reported a significant increase in lower limb pain for patients administered fluoride. In the slow-release/low dose formulations studied by Pak *et al*[6] and Reginster *et al*,[49] there was no increased risk of drug-related adverse events. Dose, formulation and regimen may play a role in fluoride's efficacy and tolerability,[49] and further clinical evidence will be required to determine the optimal combination of the three.

Calcitonin

After combining three dosages from a two-year dose-ranging study (n=208) of salmon nasal calcitonin, Overgaard *et al*[13] reported a statistically significant reduction in vertebral and peripheral fracture risk (RR=0.23, 95% CI=0.07-0.77) using the patients with fracture method. The combining of the three different dosage groups, however, appeared not to be an *a priori* decision and allowed statistical significance to be achieved where an analysis of any single dose would not have. What especially raised a question regarding the appropriateness of combining the dosages is that analy-

ses of more recent clinical trial data of calcitonin (described later in this section) have not combined dosages to assess efficacy. Thus, the study results by Overgaard *et al* did not provide clear evidence of a fracture benefit.

Two randomised clinical trials of calcitonin by Rico *et al*[55,56] reported a significant reduction in the rates of vertebral fracture, but data on patients with fracture were not reported so that the relative risk and statistical significance could be computed using the patient with fracture method. Gennari *et al*[57] examined fractures in their study, but the authors noted that the study was too small (n=82) to make any inferences regarding fracture benefit. There were, however, interim three-year and four-year clinical trial results for salmon nasal calcitonin (n=1175) published in abstracts.[14,58] For the three-year and four-year interim analyses (the trial, when completed, will have five years of follow-up), the relative risk reduction for vertebral fractures was approximately 37% (37.4% through year 3 and 35.7% through year 4) for the 200 IU dose (p=0.037 through year 3 and p=0.02 through year 4). The difference between treatment and control groups for the 100 IU and 400 IU dosages was non-significant in both the three- and four-year interim results. Dosages were not combined in these interim analyses. Of the five criteria, the quality of the randomisation process could not be assessed and the methods/results have not yet been peer-reviewed. In the abstract, it could be ascertained that fracture was likely to be the primary endpoint of the study and the relative risk reduction and statistical significance were computed using the patients with fracture method. The overall quality of the calcitonin data should be evaluated again when the full methodology and five-year results are published in a peer-reviewed journal.

Parathyroid hormone

For parathyroid hormone, fracture studies have been extremely limited. Cyclical parathyroid hormone plus sequential calcitonin versus cyclical parathyroid hormone alone over a course of two years was examined in a randomised clinical trial by Hodsman *et al*[59] but the study was relatively small (n=30), fractures were a secondary endpoint, and no significant results (p=0.078) were reported, even with the fracture rate method. A small (n=34) three-year randomised clinical trial of parathyroid hormone plus oestrogen versus oestrogen alone by Lindsay *et al*[60] examined vertebral fracture risk as a secondary endpoint. With Lindsay *et al*'s liberal definition of 'decrease in vertebral height' (i.e. a 15% reduction in vertebral height), the authors report a p-value of 0.03 for the difference between groups when examining the fracture rate, but they also report a p-value of 0.04 when examining the number of women with fracture. However, in re-examining the results with the more liberal definition, with 2 of 17 women (12%) in the oestrogen plus parathyroid hormone group suffering a fracture, and 7 of 17 women (41%) in the oestrogen alone group suffering a fracture, the relative risk is 0.29 and the chi-square=3.78 (p>0.05). The authors reported no significant findings (using the fracture rate method as well as the patient with fracture method) when the more conservative definition of 'decrease in vertebral height', i.e. a 20% reduction, was used.

Selective oestrogen receptor modulators

Although currently there are no published randomised clinical trials with a fracture endpoint for selective oestrogen receptor modulators in the peer-reviewed literature, there is a published abstract by Ettinger *et al*[61] of a 24-month interim analysis of a three-year randomised clinical trial (n=7705) of raloxifene. In that study, the authors report that the relative risk of vertebral fracture was reduced by 44% (RR=0.56, p<0.001) with raloxifene. The quality of the design and analysis cannot yet be ascertained and the study should be properly evaluated when the complete methodology and final three-year data are presented in a peer-reviewed journal.

DISCUSSION

In order for fracture efficacy from a randomised, controlled osteoporosis clinical trial to be demonstrated, it is important that all five criteria described earlier in this paper are met. Only clinical trials for two interventions have met these criteria and have clearly demonstrated that treatment can reduce the risk of osteoporotic fracture. The bisphosphonate alendronate has the greatest and most consistent impact on fracture risk, for both radiographic spine fractures and for all clinical fractures (hip, wrist and spine). Vitamin D plus calcium is the only other therapy that has demonstrated an ability to reduce the risk of hip and non-spine fractures in a randomised clinical trial, but there are no data regarding its effect on spine fracture or on vitamin D/calcium replete individuals. And finally, there are, to date, either no published peer-reviewed clinical trial fracture data, or the data are inconclusive, for other bisphosphonates, calcitonin, fluoride, calcitriol and other vitamin D preparations, HRT, vitamin D monotherapy, calcium monotherapy, parathyroid hormone and selective oestrogen receptor modulators.

Table 2. Randomised clinical trial evidence of fracture efficacy (relative risk reductions)

	Radiographic fractures	Clinical fractures		
	Spine	Hip	Spine	Wrist
Alendronate	47%	51%	55%	48%
Calcitonin	NCE	NCE	NCE	NCE
Calcitriol and other vitamin D preparations	NCE	NCE	NCE	NCE
Calcium monotherapy	NCE	NCE	NCE	NCE
Etidronate	NCE	NCE	NCE	NCE
Fluoride	NCE	NCE	NCE	NCE
HRT	NCE	NCE	NCE	NCE
Other bisphosphonates	NCE	NCE	NCE	NCE
Parathyroid hormone	NCE	NCE	NCE	NCE
Selective oestrogen receptor modulators	44%	NCE	NCE	NCE
Vitamin D + calcium	NCE	27%	NCE	NCE
Vitamin D monotherapy	NCE	NCE	NCE	NCE

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NCE, no conclusive evidence

Table 2 summarises the published clinical trial evidence on demonstrated fracture efficacy.

For randomised clinical trials that have examined the impact of intervention on vertebral fractures only, concern has been raised in the literature that observed changes in vertebral height can occur from measurement error.[52,53] Recent analyses by Melton *et al*,[54] however, suggest it is unlikely that criteria used to define vertebral fractures are a controlling influence in the likelihood that a particular study will find a result favouring one treatment over another.

Reporting and interpreting fracture rate data is an important issue and must be considered by both policy makers and physicians. According to Windeler and Lange,[19] not only are the statistical inferences made from rate data invalid, but physicians who use these data to make patient management decisions must sort through the confusing and ambiguous clinical messages they contain.

Consider the following: '20 fractures per 100 patient years' is exactly the same mathematically whether: (a) 20 patients are followed for 10 years each and they each have two fractures (i.e. 20 patients x 10 years = 200 years of follow-up and 40 fractures occur: 40/200 = 20/100) or (b) 1000 patients are observed for half a year and 100 of them have one fracture each (i.e. 1000 patients x 0.5 years = 500 years of follow-up and 100 fractures occur: 100/500 = 20/100). Both (a) and (b) provide far more detail than simply '20 fractures per 100 patient years,' yet even with such additional detail, would an average physician know how to interpret these data and use them for actual patient management?

Windeler and Lange[19] cite the oestrogen study by Lufkin *et al*[3] as an example of an osteoporosis clinical trial that uses inappropriate statistical analyses. The authors state that Lufkin *et al*'s reported fracture rate data lead to a significant result, whereas the more appropriate comparison of patients with fracture leads to a non-significant result. Windeler and Lange argue that most osteoporosis studies do not provide the reader with the number of patients with fracture and they recommend that 'until complete information and adequate analyses are available, caution seems to be justified against premature interpretation of beneficial effects' for interventions in these studies.

The double-blinded, controlled, randomised clinical trial is considered the gold standard by which we assess treatment safety and efficacy; double-blinding and random assignment to treatment or control allows for all potential confounders, especially those that are unforeseen, to be controlled for. There are data from non-experimental observational studies for some osteoporosis interventions, suggesting they may have the ability to reduce the risk of fracture.[55-58] The problem with observational studies in general, however, is that one can never be sure that all confounders and biases have been considered and controlled for in the analysis and/or design. Epidemiological study results are acceptable for hypothesis generation but, because of their limitations, physicians cannot confidently use them to guide treatment decisions. High quality, double-blinded, controlled randomised clinical trials, on the other hand, provide physicians with the information they need confidently to treat patients. In published osteoporosis clinical trial research as of October 1998, only alendronate and vitamin D plus calcium have demonstrated a fracture benefit and, of the two, alendronate has provided the greatest relative risk reduction and only alendronate has demonstrated a benefit at three clinically important sites – hip, spine and wrist.

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Paper received October 1998, accepted December 1998

Causes of Age-Related Bone Loss and Fractures

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ABSTRACT

Age-related osteoporosis is a multifactorial disorder resulting in increased bone fragility and fractures due to bone loss. The major causes of age-related bone loss are decreased calcium absorption resulting in secondary hyperparathyroidism and increased bone turnover, decreased osteoblastic activity, and, if possible, late effects of sex steroid deficiency. Because age-related bone loss has occurred over many decades before fractures begin to occur, intervention programs aimed at preventing age-related osteoporosis must be begun early.

INTRODUCTION

Involutional osteoporosis is the common, primary form of the form of the disease that occurs with increasing frequency after middle age. It is one of the most important medical disorder affecting the elderly and, because of the high incidence of fractures and their huge costs, its prevention is one of the major unresolved public health problem facing America today.

CAUSES OF FRACTURES

The morbid event in osteoporosis is fracture. Operationally, there are three independent causes of these fractures--decreased bone density, qualitative changes in bone structure, and trauma from falls. Of these, by far the most important is decreased bone density [1]. Bone strength is determined by absolute bone density, regardless of age. In the absence of severe trauma, fractures do not occur until bone density has fallen below the fracture threshold which is about 1.0 g/cm^2 for both the vertebrae and the proximal femur [2] (Fig. 1). Interestingly, this fracture threshold corresponds to the lower limit of values found in young adulthood suggesting that any degree of bone loss from peak values is pathological. With further decreases in bone density, the incidence of hip fractures and the prevalence of vertebral fractures increase further [3] (Fig. 1). Low bone density, therefore, is a necessary, but not a sufficient, cause of fracture, and the risk of fracture is a probabilistic function of a given level of bone density.

Osteoporosis: Physiological Basis, Assessment, and Treatment
Hector F. DeLuca and Richard Mazess, Editors

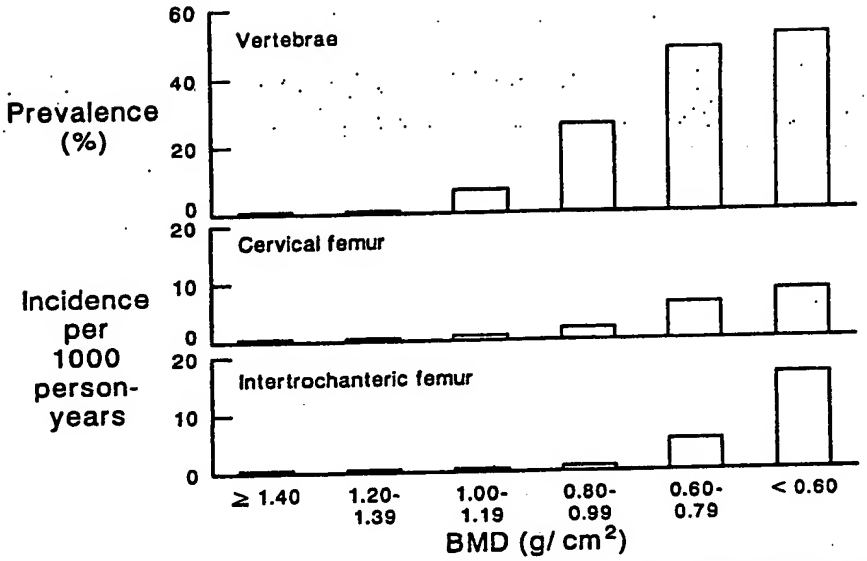

Figure 1. Occurrence of vertebral and proximal femoral fractures at various levels of vertebral and proximal femur bone mineral density (from Riggs and Melton [3], with permission of the New England Journal of Medicine).

The second cause is qualitative changes in bone structure [4] that result in a degree of bone fragility greater than would be predicted from the degree of bone loss. Possible causes of qualitative changes in bone structure with aging that could impair bone strength are listed in Table I.

Table I. Qualitative Defects in Bone That May Increase Bone Fragility.

Accumulation of microfractures
Fatigue damage
Loss of trabecular connectivity
Failure to complete secondary mineralization
Histologic osteomalacia

The third cause is trauma due to falls. With their low bone mass, fractures occur in the elderly at levels of trauma that would rarely cause injury in young persons. Indeed, the most common cause of fractures in the elderly is a fall from a standing position. Moreover, the elderly have an increased propensity to fall because of failing eyesight, arthritis, neurological diseases, muscle weakness, drop attacks, hypotensive drug use and other causes. At least one-third of elderly persons have one or more falls each year [5].

Also, the trauma of falls is increased in elderly persons because their impaired coordination and slowed reflexes decrease their ability to break the impact of falls [5]. The type of fall also may be important. Cummings [6] has suggested that posterior falls with a landing on the buttocks are particularly likely to cause hip fractures.

TYPES OF FRACTURE SYNDROMES

On the basis of evidence that is summarized elsewhere [3,7], Riggs and Melton have suggested that involutional osteoporosis can be divided into two separate syndromes (Table II). Superimposed on bone loss from these two syndromes are the effects of sporadically occurring factors that affect some, but not other individuals such as tobacco and alcohol abuses, use of drugs or occurrence of diseases that affect bone mass, and activity status [3].

Table II. The Two Types of Involutional Osteoporosis.

	Type I	Type II
Age (yr)	51-75	>70
Sex ratio (F:M)	6:1	2:1
Type of bone loss	Mainly trabecular	Trabecular and cortical
Rate of bone loss	Accelerated	Not accelerated
Fracture sites	Vertebrae (crush) and distal radius	Vertebrae (multiple wedge) and hip
Main causes	Factors related to menopause	Factors related to aging

Although the concept of two syndromes of involutional osteoporosis is not accepted by everyone, it may be serve a useful role in the examination of pathogenesis in decision making regarding therapy.

Type I (postmenopausal) osteoporosis characteristically affects women within 15 to 20 years after menopause and results from an exaggeration of the postmenopausal phase of accelerated bone loss. This syndrome is characterized by disproportionate loss of trabecular bone (Fig. 2), which results in fractures of the vertebrae and distal forearm (Colles' fracture), skeletal sites that contain large amounts of trabecular bone. The vertebral fractures usually are the "crush" type associated with deformation and pain. Accelerated bone loss occurring in type I osteoporosis is three times greater than normal in trabecular bone, but only slightly greater than normal in cortical bone. There is increased bone turnover, and bone resorption increases more than bone formation.

The major cause of type I osteoporosis is estrogen deficiency. However, only a relatively small subset of postmenopausal women develop type I osteoporosis, although all postmenopausal women are relatively estrogen deficient. Thus, some additional factor must interact with estrogen deficiency to determine individual susceptibility. The possibilities include impaired coupling of formation to resorption, increased local production of interleukin-1, or another factor that increases bone resorption, prolongation of the phase of accelerated bone loss, or some combination of these factors.

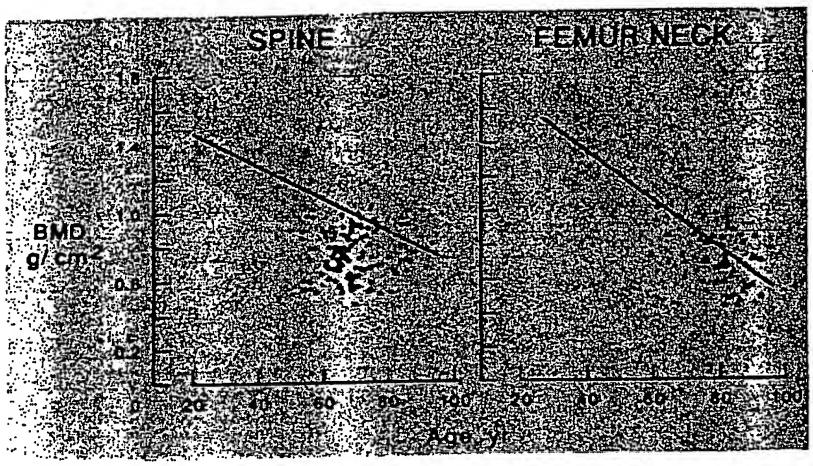

Figure 2. Bone mineral density values for lumbar spine and femoral neck. The line represents the regression on age and the cross hatched area the 90% confidence range for normal women without osteoporosis. The solid circles represent values for osteoporotic women with vertebral fractures and the solid triangles values for osteoporotic women with hip fracture. From Riggs and Melton [3] with permission of the New England Journal of Medicine.

Type II (age-related) osteoporosis occurs in both elderly men and women and is manifested mainly by hip and vertebral fractures, although fractures of the proximal humerus, proximal tibia, and pelvis also are common. Bone loss occurs gradually over many decades. In the vertebrae, this results in gradual thinning of the trabeculae causing the multiple wedge type of vertebral fractures leading to dorsal kyphosis ("dowager's hump"). Type II osteoporosis is believed to be due to factors related to the aging process.

This review will not discuss type I osteoporosis further and will be confined to causes of type II osteoporosis.

AGE-RELATED BONE LOSS

Age is by far the most important determinant of bone mass. Indeed, if the age of a healthy woman is known, it is possible to predict the bone density with a standard deviation of only about 10% [2] (Fig. 3).

Age-related bone loss probably begins in the fourth decade in both sexes and continues throughout life, or at least into extreme old age. This process occurs at a rate of about 1% per year and is slightly greater in trabecular than in cortical bone. In women, a transient phase of accelerated bone loss due to estrogen-deficiency occurs at the menopause and lasts about 4 to 8 years. This results in a loss of about 15% to 20% of trabecular bone and about 10% to 15% of cortical bone [3]. These losses are superimposed on the slow, age-related bone loss occurring in both sexes and, along with a smaller peak bone mass, account for the smaller bone mass in women and for their greater susceptibility to osteoporotic fractures. Riggs and Melton [3,7] have suggested that this slow, age-related phase of bone loss is the underlying cause of type II osteoporosis.

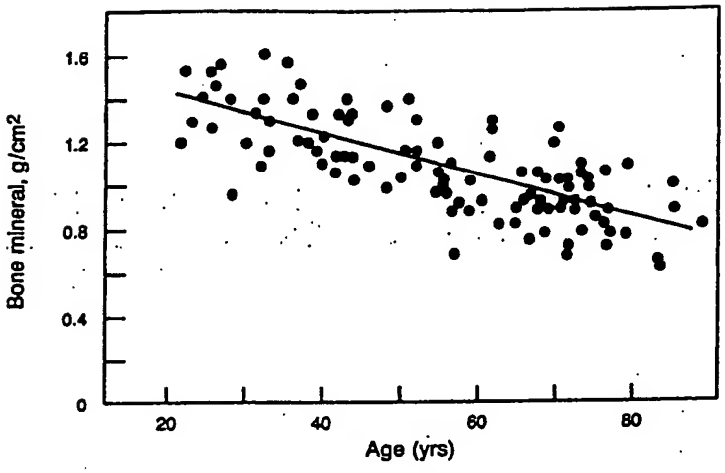

Figure 3. Effect of age on bone mineral density of the lumbar spine in 117 normal women assessed by dual photon absorptiometry (from Riggs et al. [8], with permission of the Journal of Clinical Investigation).

EFFECT OF AGE ON BONE TURNOVER

Bone remodeling occurs at discrete foci throughout the skeleton called basic multicellular units or BMUs [9]. At the beginning of each remodeling cycle, osteoclasts appear on previously inactive bone and, over a period of several weeks, construct a tunnel in cortical bone or a lacuna on the surface of trabecular bone. The osteoclasts are then replaced by osteoblasts, which over a period of three to four months, fill in the resorption cavity to create a new structural unit of bone.

Changes in bone mass are determined by the interaction of two independent processes affecting bone remodeling--the rate of bone turnover and the remodeling balance between bone resorption and bone formation [9]. The rate of bone turnover, the amount of old bone replaced by new bone per unit of time, is determined by the total number of BMUs in the skeleton at any given time. As assessed by bone histomorphometry, this is about 4% per year in normal young adults. However, in these normal young adults, there is a tight coupling of the resorption and formation phases so that changes in turnover over relatively wide ranges do not result in changes in bone mass. Bone loss implies an imbalance, "uncoupling", in the remodeling process so that there is either an increase in the resorptive phase or a decrease in the formative phase.

The elderly were formerly believed to have a decrease in bone turnover [10-12]. More recent evidence, however, suggests that they may have an increase. Some investigators have found age-related increases in serum levels of biochemical markers for bone turnover such as bone Gla-protein (BGP, osteocalcin) [13-15] and bone alkaline phosphatase [14], whereas others have not [16-18]. Whole body retention of diphosphonate, another index of bone turnover, increases with aging [19]. Although previous histomorphometric studies had indicated that older women had decreased remodeling, more recent ones employing tetracycline double labeling have suggested that, in fact, it is increased [20-22].

Despite the apparent increase in the number of new BMUs with age, there is evidence that the formative phase of the remodeling cycle is impaired. Lips and Meunier [2] found an age-related decrease in wall thickness of trabecular packets which is incontrovertible evidence of decreased bone formation at the BMU level. Thus, the elderly have a remodeling imbalance;

at each BMU, the osteoblasts fail to replace completely the bone resorbed by the osteoclasts. In the presence of a remodeling imbalance, the higher the rate of turnover, i.e., the greater number of BMUs in the skeleton, the greater the rate of bone loss.

FACTORS CONTRIBUTING TO AGE-RELATED BONE LOSS

Although it is customary to attribute bone loss to "aging", this very probably reflects the aggregate effects of several age-related processes that regulate bone cell function rather than bone cell senescence. The factors that are most likely to contribute to age-related bone loss are discussed below.

Decreased Calcium Absorption

As assessed by radioactive isotopes of calcium, absorption decreases with aging in both sexes, especially after age 65 [23-25]. The decreases have been most prominent when smaller amounts of calcium carrier have been employed, suggesting that the defect may be limited to active calcium transport, a process regulated mainly by the physiologically active vitamin D metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The impaired calcium absorption appears to be the result of two defects--increased resistance of the intestine to $1,25(OH)_2D$ action and, later in life, impaired conversion of the major circulating form of vitamin D, 25-hydroxyvitamin D (25[OH]D) to $1,25(OH)_2D$.

Although several smaller studies, including [25] one by our group have reported lower serum levels of $1,25(OH)_2D$ with aging, the largest study [26] and a recent study by us [27], have shown that serum $1,25(OH)_2D$ increases up to age 65 and then decreases or levels off. Because $1,25(OH)_2D$, the major factor regulating calcium absorption, is increasing while active calcium absorption is decreasing, this is strong evidence for resistance of the intestine to the action of $1,25(OH)_2D$. In this regard, it is of interest that intestinal $1,25(OH)_2D$ receptors have been found to be decreased in aged rats [29]. Experimental studies testing this hypothesis should now be undertaken.

The decrease in serum $1,25(OH)_2D$ levels after age 65 appears to be due to reduced activity of the renal 25(OH)D 1α-hydroxylase enzyme, which is rate limiting for $1,25(OH)_2D$ production in response to physiological needs. Decreased enzyme activity has been demonstrated directly in aged rats [30] and indirectly in elderly women [31] by measuring the response of serum $1,25(OH)_2D$ levels to infusion of synthetic PTH (1-34), a potent stimulator of enzyme activity.

Other Age-Related Hormonal Changes

Numerous investigators have shown that immunoreactive parathyroid hormone increases with age. These past data are difficult to interpret, however, because the reduction in glomerular filtration rate with aging may decrease clearance of COOH-terminal fragments of parathyroid hormone, thereby increasing circulating levels of immunoreactive species of parathyroid hormone that are not bioactive. Recently, more specific measurements have clearly demonstrated that parathyroid function, in fact, does increases with aging. Urinary cyclic AMP [13,31] and nephrogenic cyclic AMP excretion [32], both measures of biologic action of parathyroid hormone, increase with age. Although bioactive PTH, assessed by the cytochemical bioassay, did not increase with age [33], higher values in the elderly were found with the renal membrane assay for adenylate cyclase after immunoextraction of serum [34], a more precise method for detecting small increases. Moreover, serum intact PTH, as assessed by either a NH_2-terminal-specific radioimmunoassay [35] or by the two-site immunoradiometric assay [27] increased by about 50% over life. Increased secretion of parathyroid hormone with aging is the

probable cause of the increase in bone turnover previously described and, because of the coexistence of an age-related imbalance in bone remodeling, would lead to increased bone loss.

A contributory causal role of calcitonin, a potent antiresorptive hormone, has also been suggested. Patients who have undergone total thyroidectomy and who are presumably calcitonin deficient have lower bone density values than controls [36]. Several groups have shown that women have lower plasma levels of immunoreactive calcitonin than men at all ages [37,38]. Although Deftos et al. [38] reported that these levels decrease with age in both sexes, Body and Heath [39], using a method highly sensitive for monomeric calcitonin, could not confirm this finding; they did, however, confirm lower values in women.

Serum 25(OH)D, an indicator of vitamin D stores, declines moderately in the elderly [40,41] due to impaired vitamin D absorption, decreased exposure to sunlight, decreased photo dermal conversion of precursors to vitamin D, and, in some, poor nutrition. In some elderly subjects, particularly in those who are housebound with poor nutrition, histological osteomalacia may occur [42-46] (Table III). In those series that are the largest, that have the least referral bias, and that use the most rigorous histomorphometric criteria, the incidence still is appreciable in the 10 to 20% range. In addition to its effect on decreasing bone strength, vitamin D deficiency may worsen the age-related bone loss.

Table III. Proportion of Patients with Hip Fracture Whose Bone Biopsy Meet Criteria for Histologic Osteomalacia.

Series	Country	Affected, %
Aaron et al., 1974	U.K.	34
Sokoloff et al., 1978	U.S.A.	26
Lund et al., 1982	Denmark	25
Peacock and Horton, 1987	U.K.	15
Johnston et al., 1987	U.S.A.	10

Decreased Osteoblast Function

The decrease in bone formation at the cellular level that has been documented by histomorphometry, may be due to impaired regulation of osteoblast activity caused by abnormalities in either systemic or local growth factors. Serum levels of both growth hormone and insulin-like growth factor-I (IGF-I, somatomedin C), which mediates the effect of growth hormone on bone and cartilage, decline with age [47]. It is more likely, however, that the decreased osteoblast function results from impaired production of growth factors by bone cells. At least 12 local regulators of growth, produced by bone, cartilage, or marrow cells, have been identified [48]. The most important of these appear to be IGF-I, IGF-II (now known to be identical to skeletal growth factor [49]), and transforming growth factor-s. Undoubtedly, future research will be directed at defining these possible abnormalities directly.

Sex Steroid Deficiency

As discussed earlier, women have a transient acceleration of bone loss following menopause and, thereafter, resume a slow rate of bone loss that is presumed to be due to only age-related processes. However, the possibility that this slow bone loss has a component of estrogen deficiency cannot be excluded. There is indirect evidence that estrogen antagonizes the effect of PTH on bone [50] and this would be expected to potentiate the effect of the age-

related secondary hyperparathyroidism. Indeed, Quigley et al. [51] have reported that estrogen treatment slows bone loss in women who are up to 20 years postmenopausal. This important question needs further study. Although men do not undergo the equivalent of menopause, gonadal function does decline in a substantial subset of aging men [52], and it is possible that this contributes to their bone loss.

SUMMARY AND CONCLUSIONS

Osteoporosis and fractures in the elderly are common in the elderly and probably result from processes that involve the entire population of aging men and women. These processes involve slow bone loss acting over many decades. Osteoporosis is more common in elderly women than in elderly men as a result of the rapid bone loss occurring in the decade following menopause many years earlier. The slow phase of bone loss, although age-related, probably results from the summation of several age-related processes, the most important of which are summarized in Fig. 4. Because osteoporosis is more difficult to treat than to prevent, it will be important in the future to define these causal processes better and to intervene to correct them before fractures due to osteoporosis develop.

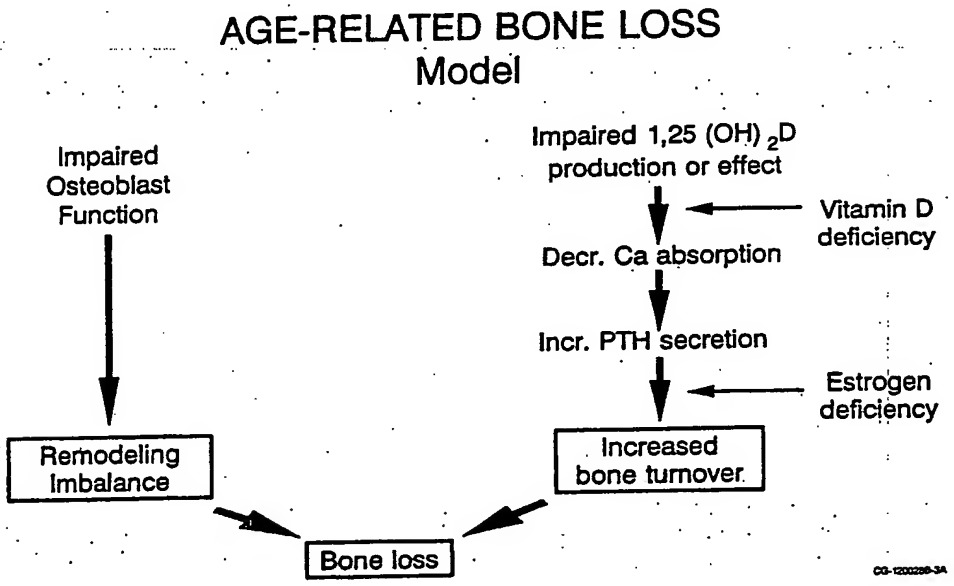

Figure 4. Model for causes of age-related bone loss.

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Osteoporosis
Physiological Basis, Assessment, and Treatment

Proceedings of the Nineteenth Steenbock Symposium held June 5 through June 8, 1989, at the University of Wisconsin–Madison, U.S.A.

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Elsevier
New York • Amsterdam • London

Elsevier Science Publishing Co., Inc.
655 Avenue of the Americas, New York, New York 10010

Sole distributors outside the United States and Canada:
Elsevier Science Publishers B.V.
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Steenbock Symposium (19th : 1989 : University of Wisconsin-Madison)
Osteoporosis: physiological basis, assessment, and treatment.

1. Osteoporosis—Congresses. I. DeLuca, Hector F., 1930- . II. Mazess, Richard B. III. Title.
[DNLM: 1. Osteoporosis—congresses. WE 250 S814o 1989]
RC931.073S74 1989 616.7'16 89-25874
ISBN 0-444-01526-4 (alk. paper)

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

Manufactured in the United States of America